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Swallowing, nutritional status and hydration in acute and sub-acute care settings: implications on survival and aspiration pneumonia

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CHAPTER 1: INTRODUCTION

Malnourishment is frequently found in hospitalized patients with a prevalence of up 50% in surgical [1], medical [2], geriatric [3, 4], and stroke [5–10] patients. This high reported prevalence is related to various factors, such as sensory losses, chewing problems, swallowing disorders and anorexia, together with acute or chronic diseases that may compromise dietary intake and lead to nutritional deficiencies and malnutrition [4]. Even if the frequency of malnutrition in hospitalized patients appears to be high, its impact on patients' outcomes and its relationships with dehydration and dysphagia are still a subject of debate [11]. In addition, the large majority of studies focused on acute stroke patients, and only limited information regarding nutrition status in patients affected by different diseases or in sub-acute care settings are available [4].

Previous reports found that poor nutrition may have serious consequences for individuals, healthcare services and society as a whole, including increased risk for morbidity, hospital admission, delayed discharge and dependence on health care [12]. In particular, Davalos et al [9] and Gariballa et al [8] found nutrition assessed after admission to be associated with mortality and dependence at 1 month after stroke. The FOOD Trial [10] investigators found post-admission nutrition to be associated with death and dependence at 6 months after stroke. A recent systematic review concluded that the odds of malnutrition were increased if dysphagia was present following stroke [13]. However, only five of the eight studies included in the review reported significant associations between dysphagia and malnutrition, and the relationship was demonstrated only in studies conducted several weeks following stroke [11]. In addition, also Crary et al [11] did not found significant association between malnutrition and dysphagia during the first week post stroke.

If the relationships between poor nutritional status and dysphagia remain ambiguous, those between dehydration and dysphagia are even less studied [14], probably because of the absence of an accepted standard for dehydration assessment. Even if prior studies reported a high prevalence of dehydration upon admission for acute stroke, and demonstrated that dehydration was associated with post-stroke complications and mortality [15, 16], only one study [11] found significant association between dehydration and dysphagia during the first week post stroke.

Finally, as far as it is concerned dysphagia, its prevalence in the general population ranges between 16% and 22% [17-19]. These findings are not surprising since the prevalence of dysphagia is high in common diseases, exceeds 50% in stroke patients, and may be as high as 84% in patients with Parkinson disease [20]. In particular, the estimated incidence of post-stroke dysphagia ranges between 29% and 79% of acute stroke survivors depending on the anatomic location of the stroke and the diagnostic or screening test used to identify this condition [21]. In patients with stroke the neurological damage may lead to absent or altered sensation, weakness, paralysis, dyspraxia, reduced postural control, altered limb movement and visual, cognitive, perceptual and communication impairments [22]. Singly or in combination, these may lead to an impairment of deglutition abilities that limits the safely ingest of adequate amounts of food and liquid thus placing the patient at increased risk for poor nutrition and/or aspiration related pneumonia. This latter may affect up to one third of patients and represents an important cause of mortality, disability and longer stay in hospital [23-25].

The relationships among dysphagia, dehydration and malnutrition, and their impact on clinical outcomes have been poorly studied and with divergent results [11-13]. In the absence of these information it appears very difficult to appropriate manage health-care resources in order to early identify the population at risk of developing negative outcomes and to develop a primary prevention program that might facilitate the clinical management of dysphagic, malnourished and dehydrated patients. In addition, even if several prognostic models for predicting negative outcomes in hospitalized patients have been developed so far [26], the large majority of them can be used only in the assessment of a specific outcome in a specific category of patients (for example the ICH score [27] in predicting spontaneous intracerebral hemorrhage after stroke). On the contrary, an ideal prognostic model should be used in populations different to those from which it was derived [28]. Moreover, to the best of our knowledge, none of the prognostic model available for predicting negative outcomes in hospitalized patients takes into account the simultaneous presence of malnutrition, dysphagia and dehydration.

In order to improve the clinical management of dysphagic, malnourished and dehydrated patients in Acute and Sub-acute care settings, this research project has been designed. In particular, the aims of the current project were: 1) to evaluate the prevalence of malnutrition, dysphagia and dehydration at admission in Acute and Sub-acute care settings; 2) to evaluate the impact of malnutrition, dysphagia and dehydration on clinical outcomes in Acute and Sub-acute care settings. Finally, the third aim of the project was to perform a statistically-based exploratory analysis (using an unsupervised clustering method) in order to identify the presence of similar phenotypic subgroups of patients according to objective criteria. In addition, the applicability of this classification system in predicting the clinical differences and the negative outcomes among the identified subgroups was also evaluated.

The relevance of this study lies in the fact that a better knowledge of the prevalence, and of the relationships among malnutrition, dehydration and dysphagia and their impact on clinical outcomes could allow a better organization of the Acute and Sub-acute Units. In addition, the identification of subgroups of patients using objective criteria could be useful for the clinicians since it could provide additional information about the patient's likelihood of develop negative outcomes, thus allowing for better disease prognosis, and helping to guide patient decision-making.

CHAPTER 2: BACKGROUND

Extract from the chapter: "Pathophysiology, Diagnosis, and Medical Management of Dysphagia" by Mozzanica F, Pizzorni N, Schindler A. Nutrition in Neurologic Disorders. 2017 [29].

Swallowing is a series of sequential coordinated events that allows passage of any substance (saliva, mucus, food, drugs) from the mouth to the stomach via the pharynx and esophagus, avoiding the passage of the swallowed substance into the airway. The term dysphagia describes any swallowing difficulty. It does not represent a medical diagnosis, but a reported symptom [30]. Different diseases may lead to dysphagia. The importance of early dysphagia recognition lies in the fact that, irrespective of the original disease, dysphagia can cause severe complications (malnutrition, aspiration pneumonia, dehydration) that severely impact patient's survival, clinical management, and health costs [31].

2.1 Swallowing Physiology

Swallowing physiology is a complex process; for teaching purposes seven stages can be identified in adults' swallowing [32–34]. The oral preparatory stage is fully voluntary and conscious in normal adults. During this phase the food is taken into the mouth, chewed and insalivated, while the largest concentration and variety of receptors of the whole body analyze taste, odor, texture, and temperature. For mastication chewing muscles elevate the mandible, the anterior neck muscles actively open the mouth, while the tongue moves the food in the molar region and the buccinators push it from the vestibulum oris. The oral transport phase begins when the bolus is considered ready to be swallowed by the sensory oral systems. The bolus is then placed in the middle of the tongue and pressed against the palate by sequential contraction. The pharyngeal phase of swallowing begins as the bolus reaches the faucial pillars and the swallowing reflex is triggered. This phase is the results of the common shared pathway between the respiratory and gastrointestinal pathways [35] and consists in changing of the pharynx configuration, from respiratory to digestive during apnea, (which is inserted in normal breathing and prevents aspiration of food into the airway) while tongue base retraction and pharyngeal peristalsis are the driving force for moving the bolus into the upper esophagus. The pharyngeal reconfiguration is related to laryngeal elevation, tilting of the epiglottis, velopharyngeal closure, velopharyngeal anteriorization, and relaxation of upper esophageal sphincter (UES). Laryngeal elevation is obtained by the contraction of suprahyoid muscles and laryngeal closure relies on intrinsic laryngeal muscles, while epiglottic tilting depends on tongue base retraction, bolus pressure, and laryngeal elevation/anteriorization. UES opening is due to laryngeal anteriorization, cricopharyngeal muscle (CM) relaxation, and bolus pressure [36]. The most common pattern of swallowing/breathing coordination is expiration-swallowing-expiration; only in rare cases, swallowing is followed by inspiration [37]. The pharyngeal phase is automatic and not conscious.

Once in the esophagus, the bolus proceeds to the stomach thanks to esophageal peristalsis, a mechanism mainly related to intrinsic nerve plexuses in the esophagus and characterized by the relaxation of the downstream smooth muscles and contraction of the upstream ones. Than, the relaxation of the lower esophageal sphincter (LES) allows the passage of the bolus into the stomach. During this phase the LES prevents reflux into the esophagus, while the pylorus avoids premature passage into the duodenum.

2.2 Neurophysiology of Swallowing

Cerebral neuronal activation influences the mechanical behavior of the pharynx and of the esophagus. The control of swallowing relies on the brain stem and the supramedullary areas. The first one is responsible for the reflex part of the swallowing mechanism: both the sensory and motor nuclei of the cranial nerves involved in swallowing as well as the interneurons connecting them lie in this part of the CNS; moreover the sequential and rhythmic patterns of motor neurons controlling the swallowing muscles are generated by a group of neurons of the medulla oblongata, called as the central pattern generator. Afferent inputs from cranial nerves V, IX, and X, of which the superior laryngeal branch, the superior laryngeal nerve, is the most important, represent one possible way to trigger pharyngeal swallowing. The brain stem sequential activity may be triggered or modulated also by the supramedullary regions including the supplementary motor area, the preand postcentral gyri, the insula, the anterior cingulate gyrus, the basal ganglia, and the cerebellum [38]. A large number of oral and pharyngeal reflexes are controlled by the neuronal connections of the brain stem and play a vital role in the complex behavior of swallowing; these reflexes modify motor neurons' activity, which receive synaptic input from supramedullary regions, and function as supporting networks of neurons assisting in the control of complex motor responses, such as speech, intraoral transport of food, chewing, and swallowing [39]. Supramedullary control of swallowing is an area of active research through animal models as well as different kinds of brain imaging techniques; although definitive understanding is not reached, five functional modules have been suggested: (1) the sensorimotor areas and the cingulate cortex establish a sensorimotor output ; (2) the thalamus, corpus callosum, inferior frontal gyrus and basal ganglia, plan the movement ; (3) the posterior parietal and premotor cortex integrate bolus information with the internal representation of swallowing movements; (4) the cerebellum facilitates the internal representation of swallowing movements and helps the movement coordination; (5) the insula, recruited for synchronizing the kinematics of the movements [40].

2.3 Pathophysiology of Dysphagia

Different diseases of neurologic and nonneurologic origin may cause dysphagia. For appropriate dysphagia management, disease diagnosis and treatment are often not sufficient, and the mechanism underlying swallowing impairment should be found.

The major signs of dysphagia are penetration and aspiration, residue along the oropharyngoesophageal tract and regurgitation either from the oropharynx into the rhinopharynx or from the esophagus into the hypopharynx. The term penetration means that part of the bolus enters the laryngeal vestibule, while aspiration means that the bolus passes the vocal folds and reaches the tracheobronchial tree. Penetration and aspiration usually cause reflexive cough, but in cases of laryngeal and/or tracheobronchial sensitivity reduction, cough may be absent (silent penetration/aspiration). Penetration/aspiration may be divided in predeglutitive, intradeglutitive, and postdeglutitive depending whether it occurs respectively before, during, or after the swallowing reflex has started [41]. While dysphagia signs confirm the presence of a swallowing impairment, the underlying mechanism should be identified for appropriate treatment [42].

Among the various nonneurologic causes that can lead to dysphagia, 2 conditions deserve a deeper description: dysphagia related to obstructive sleep apnea syndrome (OSAS) and dysphagia related to partial laringectomies.

- **Oropharyngeal dysphagia in OSAS patients**

  Extract from the article: "Oropharyngeal Dysphagia in patients with obstructive sleep apnea syndrome", by Schindler A, Mozzanica F, Sonzini G, Plebani D, Urbani E, Pecis M, Montano N. Dysphagia 2014; 29: 44-51 [43].

  OSAS is characterized by frequent episodes of occlusion of the upper airways during sleep. During these episodes, apnea (cessation of breathing) and/or hypopnea (important reduction of airflow) can occur with consequent oxy-hemoglobin desaturation. In these cases, the airway patency is reestablished through arousal from sleep [44]. Previous reports found that OSAS patients may complain swallowing problems. For example, Teramoto et al [45] reported a delayed swallowing reflex in OSAS patients, while Jaghagen et al [46, 47] demonstrated a delayed evocation of the swallowing reflex and an impairment in bolus control in snorers and OSAS patients. Teramoto et al [48] proposed the hypercapnia and the oxy-hemoglobin desaturation as possible explanation of the swallowing impairment. In addition, Valbuza et al [49], demonstrated pharyngeal stasis and premature leakage of food in OSAS. Finally, Schindler et al [43] used FEES examination in the evaluation of swallowing in OSAS patients and concluded that patients with OSAS suffer from a subclinical swallowing dysfunction, which severity is independent from the OSAS.

- **Dysphagia after partial laryngectomy**
  Extract from the article: "Functional outcomes after supracricoid laryngectomy (SCL): what do we not know and what do we need to know?" by Schindler A, Pizzorni N, Mozzanica F, Fantini M, Ginocchio D, Bertolin A, Crosetti E, Succo G. Eur Arch Otorhinolaryngol 2016; 273: 3459-3475 [50].

SCLs are organ preserving surgical techniques for the treatment of T2-T4 laryngeal carcinoma. Various subtypes of SCLs have been described according to the amount of supraglottis removed and to the extension of the resection (including or not one arytenoid) [51]. The advantages of SCLs are related to the preservation of laryngeal function (such as phonation, respiration and swallowing), by sparing at least one functioning cricoarytenoid joint [52-55]. As far as it is concerned the swallowing function, heterogeneous outcomes have been reported so far. During the first postoperative month, 30 to 100% of patients complain aspiration [54, 56-58]. In 15-80.4% of these cases [59-60] aspiration resolves spontaneously within 6 months after the surgery. Normal oral diet is achieved normally within 12 months after SCL even if occasional aspiration (normally well tolerated) have been reported in up to 67% of patients [55, 61-66].

2.4 Complications of Dysphagia

Dysphagia complications include but are not limited to aspiration pneumonia, malnutrition, dehydration, and chronic aspiration; while pulmonary complications are the result of impaired safety of swallowing leading to tracheobronchial aspiration, malnutrition and dehydration are due to impaired efficacy of swallowing with reduced oral intake of nutrients

- **Aspiration Pneumonia**

  Pulmonary complications are probably the most common and severe complications of dysphagia. They are the results of an impaired balance between defense mechanisms of the lower respiratory tract, oropharyngeal bacterial colonization, and impaired efficacy of swallowing with aspiration of the bacteria [67]. The lower respiratory tract is protected by several defense mechanisms: airway clearance, including mucociliary action, cough, cellular immune defense by macrophages, lymphocytes, and neutrophils, and lymphatic clearance. Several clinical conditions can reduce these defense mechanisms, increasing the risk of pulmonary complications whether food or liquid aspiration occurs. Among pulmonary complications, aspiration pneumonia is defined as the development of an infiltrate in the dependent portions of the lung in people who are at increased risk for aspiration of oropharyngeal contents (microaspiration) containing bacteria with associated symptoms and signs of lung infection [68]. Different papers showed an increased relative risk of developing pneumonia in patients with aspiration; however, the role played by the various risk factors was not equal in the different populations [69–74]. Other factors, such as advanced age, medical conditions, mental status, poor nutritional status, and oropharyngeal colonization of pathogenic bacteria appeared as risk factors for developing aspiration pneumonia [75]. The role of oral care has been investigated in a series of studies [76–78]; it has been demonstrated that oral care reduces pneumonia and death from pneumonia in both dentate and edentate patients [78].

- **Dehydration**

Dehydration is frequently reported in hospitalized or institutionalized patients. Clinical, institutional and sociocultural factors may cause an inadequate fluid intake [79]. When the presence of dysphagia is recognized and aspiration of thin liquids is reported through an instrumental assessment of swallowing, thickened liquids are often recommended [80], in particular when a coexisting language and/or cognitive impairment reduce the possibility to effectively use compensatory strategies (e.g., postures) that may reduce aspiration of thin liquids. Despite the reduction of liquids' aspiration, different studies report an inadequate liquid intake (<1500 ml/day) in poststroke patients requiring thickened liquids [81–84], while the positioning of enteral nutrition has a significant and positive impact on dehydration in patients with severe dysphagia [82]. Factors associated with poor fluid intake in poststroke patients with thickened liquids are the presence of functional deficits in cognition reducing the compliance with clinicians' recommendation, the frequency of beverage offerings and the availability of thickened liquids to patients, and the inaccurate preparation of thickened beverages, often too thick [83]. Therefore, fluid intake in poststroke dysphagic patients could be increased with protocols for the provision and monitoring of thickened liquids' consumption, through an adequate education of nursing staff and caregivers, and by integrating hydration using nonoral supplementary routes.

- **Malnutrition**

  Malnourishment is common in hospitalized patients with a prevalence of up to 50% in surgical, medical, geriatric, and stroke patients [85]. This reported high prevalence is related to a several factors that singly or in combination may facilitate nutritional deficiencies [5, 85]. As far as the swallowing problems are concerned, the relationship between dysphagia and malnutrition is debated. A recent review reported that the odds of malnutrition were increased in elderly, frailty and institutionalized persons, in patients with excessive polypharmacy, general health decline, cognitive decline, eating dependencies, and dysphagia [13, 86]. It must be noted that 5 out of the 8 studies included in the review demonstrated a relationship between malnutrition and swallowing. In addition, the pooled analysis revealed a significant effect only for trials conducted several weeks following stroke.

- **Chronic Aspiration**

  Chronic aspiration may not cause acute infections within the lungs (aspiration pneumonia) but can lead to diseases such as chronic lipoid pneumonia, obliterative bronchiolitis, and diffuse aspiration bronchiolitis. Typically, the aspiration is silent, and the patient often presents with slowly progressive symptoms of cough, shortness of breath, recurring fevers, and lung opacities on chest radiograph. On CT scan the disease usually presents as diffuse basilar centrilobular nodules and/or treeinbud pattern with airway and interstitial thickening. Often the diagnosis is not elucidated until biopsy reveals granulomatous inflammation associated with particulate matter consistent with oral or gastric origin, such as vegetable, lipid, or talc particles. Chronic occult aspiration has been associated with refractory asthma and idiopathic pulmonary fibrosis [87].

2.5 Dysphagia Assessment

Dysphagia assessment is of pivotal importance not only for the search of the etiology but also to identify patients with dysphagia, recognize its severity, estimate risk of complications, and provide the most appropriate management.

- **Screening**

  Extract from the article: "Dysphagia screening in subacute care settings using the Italian version of the Royal Brisbane and Women's Hospital (I-RBWH) dysphagia screening tool" by Mozzanica F, Scarponi L, Pedrali S, Pizzorni N, Pinotti C, Foieni F, Zuccotti G, Schindler A. Acta Otorhinolaryngol Ital 2017; 37: 25-31 [88].

  The estimated incidence of dysphagia in hospitalized patients ranges between 15% and 30% [89, 90]. These findings are not surprising since the prevalence of dysphagia is high in common diseases - it exceeds 50% in stroke patients, accounts for 10-30% of individuals older than 65 years [91] and may be as high as 84% in patients with Parkinson disease [20, 92].

  Dysphagia limits the safely ingestion of adequate amounts of food and liquids thus placing the patient at increased risk for poor nutrition, dehydration, aspiration pneumonia and morbidity in general [12, 93]. In addition, patients affected by dysphagia experience an increased risk of hospital admission, delayed discharge and dependence on health services (for example increased nursing time and physician consultations) thus increasing health care costs [33, 94]. For these reasons, the early identification of dysphagia is mandatory since it can reduce the incidence of clinical complications and may improves the outcome in these patients [95-97]. Even if clinical and instrumental assessment using either videofluoroscopic swallowing study (VFSS) or fiberoptic endoscopic evaluation of swallowing (FEES) is considered the "gold standard" for the identification of swallowing dysfunctions [98-100], this approach presents some limitations. Instrumental assessment is usually not available on a 24-hours basis and not all the patients can be carried to the radiology department and correctly positioned, even with specially adapted chairs [101, 102]. It appears consequently difficult to assure a well-timed screening of dysphagia, especially outside the standard working hours on weekdays. Moreover, instrumental assessment is usually not available at patient admission. In order to take decisions on feeding for newly admitted patients and to reduce the number of patients requiring VFSS or FEES and prevent dysphagia related complications, several dysphagia screening tools have been proposed [88, 90, 103].

The large majority of dysphagia screening tools have been developed for stroke population and only few screening tools for patients with different diagnosis are available [104]. One of the more complete is the Royal Brisbane and Women Hospital (RBWH) dysphagia screening [90]. This latter is a nurse-administered, evidence based swallow screening tool for generic acute hospital use and it is based on the triaging concept. It consists of three steps: 1. a two-phase question screen; 2. a water swallow test, as appropriate; 3. a swallowing management plan.

In the first phases the nurse explores the presence of medical diagnosis associated with swallowing problems (for example head injuries, stroke, head and neck surgery) [105]. A positive indicator for any of the medical diagnosis associated with dysphagia prompts the nurse to complete phase 2. The latter collects information related to feeding and swallowing problems. If present, the patient is placed nil by mouth and referred to the speech and language pathologist for swallowing assessment. On the other hand, patients who did not report feeding or swallowing problems are administered a water swallow test with 90 ml of water. In the original study of Cichero et al [90], the RBHW dysphagia screening tool demonstrated a sensitivity of 95%, a specificity of 97%, a positive predictive value of 92%, a negative predictive value of 98% when compared to formal clinical assessment. An Italian version of the RBWH (I-RBWH) dysphagia screening tool was developed recently [88]. The process of cross-cultural adaptation and validation into Italian comprised 4 phases: item generation (phase 1), nurse training (phase 2), reliability analysis (phase 3) and screening accuracy analysis (phase 4). The tool was tested on a group of 105 consecutive patients admitted to the SubAcute Care Unit of L. Sacco Hospital. Similar to the original version also the I-RBWH dysphagia screening tool has good reliability and screening accuracy with a sensitivity of 93%, specificity of 96%, positive predictive value of 90% and negative predictive value of 97%.

- **Bedside Evaluation (BSE)**

  The bedside examination (BSE) is the clinical assessment performed by a swallowing expert, usually a speech and language pathologist, without the support of any instrument; the aims are to detect the presence of an alteration of the swallowing process, to decide how to provide nourishment to the patient, to set the rehabilitation goals and program, and to underline the need of an instrumental assessment. The BSE also includes the assessment of aspects different from swallowing, guiding the clinician in the identification of possible barriers, facilitators, and patient's resources. The BSE should include:

  Collection of anamnestic data, i.e., diagnosis, medical history, previous clinical and instrumental assessments of dysphagia, rheological modifications of liquids and foods, and recent modification of nutritional status, respiratory status, alcohol abuse;

  Observation of vigilance, communication efficacy, presence and characteristics of tracheal cannula, sialorrhea, oral hygiene, presence of neglect, auditory and visual defects, and independence;

    - Morphodynamic assessment of swallowing structures (the lips, tongue, hard and soft palate, jaw, larynx, and head and trunk control);
    - Oral praxis assessment;
    - Sensitivity assessment;
    - Normal reflexes assessment (cough, gag, and swallowing reflex);
    - Pathological reflexes assessment;
    - Swallowing trials with different consistencies and volumes.

  Several studies have demonstrated that as nowadays there still exists an inconsistency in the clinical assessment of dysphagia [106, 107]. However, different protocols including all the aspects that should be investigated during the BSE are available in literature. In particular, one of the most widespread protocols is the Mann Assessment of Swallowing Ability (MASA) [108]. After BSE the main pathophysiologic signs of impaired swallowing can be detected; however, pathophysiologic interpretation of signs may be difficult. Moreover, silent aspiration cannot be detected.

- **Instrumental Assessment of Swallowing**

The aim of instrumental assessment of swallowing is to perform a thorough assessment of swallowing in order to understand whether a disorder is present, oral feeding is safe, or rehabilitation is necessary. In order to perform instrumental assessment, specific knowledge and skills are necessary; if the examiner holds only part of the requested knowledge and skills, an incomplete examination is performed, the information obtained will be misleading, the prescription inadequate, and the clinical decision potentially wrong. The acronym FEES (fiberoptic endoscopic evaluation of swallowing) is usually applied to mean the assessment of swallowing thanks to a flexible endoscope. FEES may be performed in different settings: at the bedside, in the office, and at home; depending on the circumstances, instrumentation may vary, but a fiberscope and a light source are always needed. The procedure to perform FEES may be divided into five major steps: swallowing structures anatomic assessment; swallowing structures' sensorimotor assessment, secretion management, bolus transit assessment with foods of different volumes (5 cc, 10 cc, 20 cc), and consistency (thin liquid, nectar, honey, puree, soft solid, solid); response to therapeutic maneuvers; and interventions to improve swallowing. All the swallowing structures should be fully observed including the rhinopharynx, the velum, the oro- and hypopharynx, the larynx, the upper part of the trachea, the pyriform sinuses, and the retrocricoid region, the tongue base, and the valleculae. The assessment of swallowing structures' motion is of key importance as it gives information on the neuromotor functionality of the system; it includes specific maneuvers to examine individual movements such as blowing to assess velopharyngeal movements, squeezing maneuver (high pitch strained voice) to assess pharyngeal wall motion, breathing, voicing to assess laryngeal movement, and Valsalva maneuver to assess laryngeal vestibule closure. In order to assess laryngeal sensibility, the tip of the scope could gently touch the epiglottis, the arytenoids, the laryngeal vestibule, and the vocal folds. In the presence of secretions, its characteristics (serous, mucus), site (oro/hypopharynx, larynx), and spontaneous or induced management are also of key importance to understand the physiology of swallowing structures. The most important part of the FEES is the assessment of bolus transit: the scope could be positioned just below the velum (high position) or close to the laryngeal vestibule (low position), according to whether the examiner is more interested in a general view of the pharynx and larynx or is more focused on the larynx. At least three food consistencies should be used (liquids, puree, solid), with increasing volumes for each consistency. One of the major advantages of FEES is its versatility as any kind of food could be tested. Finally, the main postures and maneuvers according to their specific rationale (see following chapter) should be tested in case a swallowing impairment is found. In selected cases FEES can also be used for rehabilitation as a biofeedback system. During bolus transit, FEES does not allow to see the bolus itself. In fact, as the bolus enters the oropharynx, the pharyngeal phase of swallowing is triggered, and the pharynx changes its configuration from respiratory to swallowing: the tongue base retracts, the pharyngeal wall is squeezed, and the vision is lost (socalled whiteout phase). As the respiratory configuration of the pharynx is restored, the whiteout phase ends, and the bolus is already in the esophagus. The main abnormal findings include (1) anticipated passage of the bolus from the oral cavity to the oro- and hypopharynx; (2) pooling of the part of the bolus in the oral cavity, in the valleculae or in the pyriform sinuses; (3) penetration and aspiration; (4) regurgitation from the oropharynx in the rhinopharynx; and (5) regurgitation from the esophagus into the pharynx. The understanding of the underlying mechanism is of key importance for the interpretation of FEES [109].

The videofluoroscopic swallow study (VFSS) is a radiologic technique providing a comprehensive evaluation of the oral, palatal, pharyngeal, pharyngoesophageal, and esophageal segments of swallowing. The patient is positioned upright in an examination chair within the fluoroscopy unit in the lateral position and then in anteriorposterior view. The protocol proceeds in a stepwise fashion. Patients are administered with liquid, nectar, honey, and puree barium of precise aliquot of increasing volumes; bariumcoated solids are also administered. For each bolus the patient is asked to hold the bolus in the oral cavity and swallow when asked to; the whole process is videorecorded with a frame rate of 25–30 frames per second, in order to interpret the examination after the examination and not while performing it. Framebyframe analysis is often necessary for precise interpretation of the VFSS. During VFSS not only the contrast bolus is clearly visible but also the following structures and their movements: the lips, mandible, maxilla, tongue, velum, hyoid bone, vallecula, epiglottis, arytenoid cartilage, false vocal folds, true vocal folds, laryngeal vestibule, pyriform sinuses, pharyngeal muscles, CM, trachea, and cervical spine. Abnormal findings assessed through VFSS include prolonged oral preparation time, tongue pumping due to difficulty in triggering the pharyngeal phase, and serial swallows also known as piecemeal deglutition due to weakness of the oral and pharyngeal musculature, poor bolus formation, oral stasis, poor mastication, nasal regurgitation, delayed swallowing reflex, penetration/aspiration, reduced hyoid elevation, reduced laryngeal elevation, vallecular or pyriform residue, deviant epiglottic function, reduced laryngeal elevation, cricopharyngeal bar due to a defect in cricopharyngeal opening or closing, pharyngeal diverticula, esophageal diverticula, strictures and rings, and esophageal motor impairment.

FEES and VFSS can be considered the two frontline instrumental examinations to assess a person with a potential or known swallowing impairment; both FEES and VFSS can be used to test treatment strategies. These two examinations should not be considered overlapping but rather complementary, as the information they provide are not the same. VFSS allows better assessment of oral phase, allows assessment of esophageal phase, and should be considered the optimal examination, especially for cricopharyngeal dysfunction evaluation; on the other side, FEES allows better definition of residue, penetration, and secretion management; besides, FEES can be prolonged and is a better examination for assessment of fatigue. Finally, FEES can be performed consecutively as needed and in almost any setting, regardless of patient positioning and general conditions [110].

- **High Resolution Manometry**

High resolution manometry (HRM) is a diagnostic system that measures intraluminal pressure activity in the gastrointestinal tract from the pharynx to the stomach using a series of closely spaced pressure sensors during 5 ml of liquid swallow. HRM provides a topographic mapping of the spacetime patterns of hypopharyngeal pressures by means of colored contour plots emerging from 36 sensors spaced at 1 cm interval. Three dimensional data are displayed on a two dimensional planar surface: the pressure levels as color bars (mmHg), the sensor position (cm) on the y axis, and the time (s) on the x axis. Mainly developed for esophageal diagnostics, its application in the pharynx is getting an increasing importance. For this purpose, the oropharyngeal swallowing process can be viewed as a pressure generation mechanism powered by a two pump system, the oropharyngeal propulsion pump and the hypopharyngeal suction pump. The oropharyngeal pump reflects the combined activity of the tongue base muscles and the upper pharyngeal constrictor muscles, while the hypopharyngeal suction pump reflects the suction forces in the pharyngeal chamber which are the result of the anterocephalad movement of the hyoidlaryngeal complex. At that same instant, the CM relaxes, enabling traction forces to open it, while the lower pharyngeal constrictor muscles push the bolus into the esophagus. Various features can be defined, such as the UES resting pressure, duration of UES relaxation, nadir pressure during relaxation, duration and pressure of UES post relaxation contraction, peak pharyngeal pressure, intrabolus pressure, and the coordination of the pharyngeal peak within the UES relaxation period [111].

Other Assessment Tools While FEES and VFSS represent the two gold standard techniques, other instrumental tools have been developed. Each of them can have a diagnostic role for specific clinical conditions but may be misleading if not applied after clinical examination and either FEES or VFSS. The two most important instrumental assessment tools besides those previously described are the oropharyngoesophageal scintigraphy (OPES) and the electromyography of swallowing (EMGS). During OPES the patient is given liquid or semisolid with the radionuclide technetium99 and is asked to swallow while placed under a gamma camera. Thanks to the gamma camera, a quantitative picture of radionuclide transit and metabolism can be shown as a plot of radioactivity versus time, while OPES has suboptimal temporal and anatomical resolution, it represents the ideal tool for quantification of residue and aspiration [112]. EMGS allows optimal analysis of muscle contraction duration. Usually EMGS includes surface EMG of submental muscles, needle EMG of the CM, and application of a mechanical transducer on the larynx; simultaneous recording from these three lines allows optimal temporal analysis of submental muscle contractions, laryngeal elevation, and cricopharyngeal relaxation. EMGS is the optimal technique for the identification of CM relaxation impairment that may be treated through botulinum toxin injections [113].

- **Quality of life (QOL) assessment**

Extract from the articles: "Cross-Cultural Adaptation and Validation of the Italian Version of SWAL-QOL" by Ginocchio D, Alfonsi E, Mozzanica F, Accornero AR, Bergonzoni A, Chiarello G, De Luca N, Farneti D, Marilia S, Calcagno P, Turroni V, Schindler A. Dysphagia 2016; 31: 626-634 [114]; and "Reliability and validity of the Italian Eating Assessment Tool" by Schindler A, Mozzanica F, Monzani A, Ceriani E, Atac M, Jukic-Peladic N, Venturini C, Orlandoni P. Ann Otol Rhinol Laryngol 2013; 122: 717-724 [115].

Even if VFS and FEES are considered the gold standard in the evaluation of a patient with dysphagia, these examinations can not provide information regarding the patient's perspective about his/her disease. The latter may influence clinical decision and could be used to monitor individual patients' outcome [116-123]. Previous reports highlighted the influence of swallowing problems on patient's quality of life (QOL). For example, Eslick et al [120] reported a significant relationship between swallowing and emotional disorders such as anxiety and depression; while Ekberg et al [121] found that 41% of dysphagic patients have complained panic or anxiety during mealtimes.

Several swallowing-related QOL measurements have been developed so far [124-133]. The most widely used it the SWAL-QOL. The latter is composed by 44 items, grouped in 11 subscales, exploring different aspects of the patient's QOL [124]. This questionnaire demonstrated good psychometric qualities [125], has been used in different outcomes [126-128] and has been translated into other languages, e.g., French [129], Dutch [123, 130], Swedish [119] and Italian (I-SWAL-QOL) [114].

An other useful instrument for the assessment of QOL in patients with dysphagia is the Eating Assessment Tool-10 (EAT-10) [133]. It consists of 10 questions, it is easily administrable and demonstrated good reliability and validity. An Italian version of this tool has been developed recently (I-EAT-10) [114]. The latter demonstrated optimal internal consistency, test-retest reliability and clinical validity.

2.6 Management of Dysphagia

As stated in the introduction of this chapter, dysphagia is not a disease, but it is a symptom or a sign of a given disease. Management of dysphagia starts with adequate diagnosis and provision of the best treatment available of the underlying disease. Although dysphagia is often caused by neurological diseases for which no significant treatment is available, as in the case of motor neuron disease, in some other cases, a pharmacological treatment can dramatically improve the clinical condition, as, e.g., in myasthenia gravis. It is therefore imperative to properly treat all neurological diseases, keeping in mind that improvement in neuromuscular function might impact swallowing also; for example, LDOPA can improve movements in patients with Parkinson's disease and, if given before mealtime, can improve swallowing also too.

- **Pharmacological Treatment**

  Swallowing physiology relies on a complex neuromuscular chain of events, regulated by a network of neurons throughout the brain; it is therefore theoretically possible to improve swallowing function pharmacologically acting on the regulation of the neurotransmitters involved in these systems. While research is trying to move forward in this direction, especially stimulating the availability of substance P for glossopharyngeal and superior laryngeal nerve, eventually using irritants to the pharynx as capsaicin, there is no evidence in the application of a pharmacological treatment in clinical practice [134] and no pharmacological treatment to improve swallowing is available so far. On the other hand, several medications could have undesirable effects on swallowing, such as xerostomia. The latter may impair the bolus transport and increase the residue of food during swallowing. Also pharmacological treatment with calcium channel blockers, nitrates, and benzodiazepines may facilitate dysphagia by causing gastroesophageal reflux disease [135].

- **Botulinum Toxin**

  Botulinum toxin blocks the release of acetylcholine from the cholinergic nerve endings with inactivation of glands and muscles. The effect is transient and depends on the frequency and dose of administration [136]. In the field of swallowing disorders, the toxin can be injected into the salivary glands under ultrasound guidance for the treatment of drooling. The latter may occur in patients with neurogenic dysphagia including those with cerebral palsy, myasthenia gravis, Parkinson's disease and amyotrophic lateral sclerosis. The reduction of salivary secretion may last for five months [137]. An other interesting application of the botulinum toxin is in the treatment of CM incoordination. CM dysfunction may result from a delay or failure of relaxation of the fibers during deglutition. Often the underlying cause is not treatable, or it remains unknown. In these cases, EMGguided botulinum toxin injections to the muscle can be performed either percutaneously [138] or endoscopically [139] and have been found to be effective in the treatment of this selective kind of dysphagia [140].

- **Adjuvant therapy**

  Extract from the article: "Neuromuscular Electrical Stimulation for Treatment-Refractory Chronic Dysphagia in Tube-Fed Patients: A Prospective Case Series" by Scarponi L, Mozzanica F, De Cristofaro V, Ginocchio D, Pizzorni N, Bottero A, Schindler A. Folia Phoniatr Logop 2015; 67: 308-314 [141].

Even if traditional swallowing therapy (TT) represent the first step in the management of dysphagic patients [142], TT has varying degrees of success [143]. For this reason, several adjuvant therapies [144-148] have been proposed so far. One of the more interesting among them is the neuromuscular electrical stimulation (NMES) [148]. The aim of the NMES is to improve the strength of the oropharyngeal muscles and their patterned activity, by neuromuscular stimulation.

Previous studies reported diverging results about NMES therapy [149-157]. In particular, Bulow et al [150] did not find any significant difference in the swallowing results after NMES or TT treatment. Humbert et al. [151] demonstrated that electrical stimulation may reduce hyolaryngeal elevation in healthy. On the other hand, Miller et al [149] demonstrated the NMES efficacy in the adjuvant therapy of vocal fold paresis; while Scarponi et al [141] demonstrated that NMES in adjunctive to TT significantly improved the swallowing functions in severe dysphagic patients refractory to TT.

- **Surgical Treatment**

Extract from the article: "Functional fat injection under local anesthesia to treat severe post-surgical dysphagia, a case report" by Ottaviani F, Schindler A, Klinger F, Scarponi L, Succo G, Mozzanica F. Head and Neck 2017 in press.

Severe dysphagic patients with chronic aspiration and/or recurrent aspiration pneumonia, who failed an extensive nonsurgical swallowing rehabilitation, require a strict tube feeding regimen, either by means of a nasogastric tube or a percutaneous gastrostomy tube. However, this will not always result in a complete abolishment of chronic aspiration, as the production and swallowing of saliva will still continue; in addition, lifetime tube feeding is often considered unacceptable for many patients. For this reason, several surgical procedures aimed to the restoration of oral intake have been proposed [159]. UES myotomy can be useful in patients affected by UES dysfunction, while partial pharyngectomy was found to be effective in patients affected by pharyngeal hemiparesis [160]. However, in patients with severe aspiration, inadequate deglutition coordination and diminished laryngeal sensation, more drastic procedures, such as total laryngectomy or other procedures of tracheoesophageal separations, are required. The result is a permanent anatomic separation of the airway and digestive tract with the invariable loss of normal voice and respiration [161]. A valuable alternative to tracheoesophageal separation procedures is the laryngeal elevation in which the larynx is permanently fixed in the position that would normally be obtained during the pharyngeal phase of swallowing. The suspension of the larynx protects the airways from aspiration since the epiglottis is lowered over the laryngeal vestibule, and the larynx is pulled out of the way of the food bolus' path. In addition, because the UES is attached to the larynx, anterior and cranial displacement of the larynx results in the opening of the esophageal inlet, thus facilitating the passage of the food bolus. Laryngeal elevation was found to be effective in dysphagic patients with severe aspiration caused by deficient laryngeal elevation, insufficient opening of the UES, and lack of pharyngeal constrictor activity. In these patients, laryngeal elevation could be considered a valuable alternative to more drastic procedures [161]. An other promising technique recently proposed is focused on polydimethylsoloxane or fat injections for the treatment of selected patients with severe dysphagia [162, 163]. In particular, Kraaijenga et al [163] reported their promising experience with lipofilling of the tongue base in the treatment of six head and neck cancer (HNC) patients with chronic dysphagia secondary to surgery and/or chemoradiotherapy. Also Navach et al [164], reported satisfactory swallowing results after lipofilling of the tongue base in a patient treated with radiation therapy for a nasopharyngeal carcinoma and consequent severe post-radiation dysphagia.

CHAPTER 3: PROJECT AIMS

The aims of the current projects were

PHASE 1: To appraise the prevalence of malnutrition, dysphagia and dehydration at admission in Acute and Sub-acute care settings.

PHASE 2: To assess the association between malnutrition, dysphagia and dehydration at admission and short and long-term outcomes in hospitalized patients both in Acute and Sub-acute care settings.

PHASE 3: To perform a statistically-based exploratory analysis (using an unsupervised clustering method) in order to identify the presence of similar phenotypic subgroups of patients according to objective criteria and to evaluate if this classification system could predict clinical outcomes.

Project hypothesis:

The prevalence of malnutrition, dehydration and dysphagia is hypothesized to be high in acute and sub-acute care settings. Nutritional deficits, dehydration and swallowing impairment are expected to influence clinical outcomes. Dysphagia could play a role in the development of malnutrition and dehydration. The application of a statistically-based classification system could help clinicians in predicting negative outcomes.

Project relevance:

A deeper understand of the prevalence and of the relationships among malnutrition, dehydration and dysphagia and their impact on clinical outcomes could allow a better organization of the Acute and Sub-acute Units. In addition, the identification of subgroups of patients using objective criteria could be useful for the clinicians since it could allow an easier identification of patients at risk of poor clinical outcomes.

CHAPTER 4: MATERIALS AND METHODS

As the current project is structured into different phases, in this section, the materials and methods of the different phases are presented. For patient's assessment, only validated instruments have been selected in order to facilitate comparisons with other studies and future researches.

4.1 Materials and methods of Phase 1

The aim of the first phase of the project was to evaluate the prevalence of malnutrition, dysphagia and dehydration at admission in Acute and Sub-acute care settings.

Population

In a period of three years, a total of 686 patients were recruited, 483 of them were admitted to the Acute care Unit (Stroke-Unit), while 203 were admitted to the Sub-acute care Unit. Written informed consent for functional and laboratory measurements, including blood testing were obtained on admission from all patients or those authorized to give consent for them. The study was performed according to the declaration of Helsinki and it was previously approved by the Institutional Review Board of our hospital. Inclusion criteria for patients in Acute care Unit were: diagnosis of stroke confirmed by magnetic resonance imaging and/or computed tomography and no history of neurologic disorders, previous stroke, swallowing disorders, head and neck trauma or surgery. As far as the Sub-acute care Unit is concerned, inclusion criteria were: patients with acute illness, injury or exacerbation of a disease process who needed treatment for one or more specific active complex medical conditions or needed the administration of one or more technically complex treatments, in the context of a person's underlying long-term condition and overall situation.

Collected variables

Information regarding age, gender, weight, height, presence of aphasia and dysarthria, severity of stroke (only in patients admitted to the Acute care Unit and assessed through the NIH stroke scale, NIHSS [165]), data on functional status activity of daily living (assessed through Barthel Index, BI [166]), and data on oral intake (assessed through the Functional Oral Intake Scale, FOIS, [167]) were also collected

at admission as well as information regarding presence of dysphagia, malnutrition and dehydration. For statistical analysis NIHSS, BI and FOIS scores were dichotomized (cut-off scores of 8 for NIHSS, 75 for BI and 6 for FOIS).
As far as it is concerned the swallowing evaluation, each patient was evaluated by nursing staff using the the Italian version of the Italian version of the Royal Brisbane and Women's Hospital (I-RBWH) dysphagia screening tool [88, 90]. The latter consists of (1) a two-phase question screen, (2) a water swallow test, as appropriate, and (3) a swallowing management plan. The two phases of the tool reflected the perception that identification of 'at-risk' patients should come from a combination of (1) previous medical history/records and (2) specific clinical indicators. If any of the dysphagia indicators are present, the patient is placed nil by mouth (NBM) and referred to Phoniatric Unit for formal dysphagia assessment. Individuals without dysphagia indicators are administered a water swallow test with 90 ml of water. In our sample the patients who resulted positive in the dysphagia screening examination were referred to the speech and language pathologist (SLP) who performed a bedside evaluation and, if needed, to the phoniatric department in order confirm the presence of dysphagia through a Fiberoptic Endoscopic Evaluation of Swallowing (FEES) [168, 169].
Clinically relevant malnutrition was defined following the consensus-based minimum set of malnutrition criteria proposed in 2015 by the European Society for Clinical Nutrition and Metabolism [170]. The ESPEN consensus group suggests that a patient is only considered to be malnourished if the weight loss had led to a considerable depletion of energy or protein reserves, represented by BMI or FFMI below the suggested cut-off points. A patient with unintentional weight loss but with (still) normal energy and protein reserves is considered to be a patient at risk, but not yet malnourished [171]. Consequently, patients were considered malnourished if they have been identified as being at risk for malnutrition (using the Malnutrition Universal Screening Tool, MUST [172]) and had a BMI of <18.5 kg/m2 or a combination of unintentional weight loss (>5% weight loss over the last three months) and a BMI of <20 kg/m2 (<22 kg/m2 in patients 70 years and older).
Finally, as far as the dehydration assessment is concerned, the BUN/Cr ratio was used. This latter is considered the best indicator of dehydration commonly available [173, 174] and represents the ratio of two serum laboratory values, the blood urea nitrogen (BUN) (mg/dL) and serum creatinine (mg/dL) (Cr). The principle behind this ratio is the fact that both urea (BUN) and creatinine are freely filtered by the glomerulus,

however urea reabsorbed by the tubules can be regulated (increased or decreased) whereas creatinine reabsorption remains the same (minimal reabsorption). BUN/Cr ratios > 20 indicate under hydration [173]. The BUN/Cr was assessed from blood samples obtained on the day of hospital admission.

Statistical analysis

Statistical analysis: mean ± standard deviation (SD) and percentages were used when appropriate in order to describe continuous and categorical data. Student t test and Chi-square test were used to compare the distribution of continuous and categorical data among patients according to gender and presence of dysphagia. The Phi test was used to evaluate the presence of significant correlations among the continuous variables. A significant level of $p < 0.05$ was used for all the comparisons.

4.2 Materials and methods of Phase 2

The aim of the second phase of the project was to assess the association between malnutrition, dysphagia and dehydration at admission and negative outcomes in hospitalized patients both in Acute and Sub-acute care settings. In addition, since several previous studies have shown that unintentional weight loss in patients leads to a higher mortality risk [175-180], additional information regarding critical weight loss (CWL), defined as > 5% weight loss in the previous month and/or >10% weight loss in the previous six months [181], were also collected in order to investigate also the impact of CWL in combination with malnutrition, dysphagia and dehydration in negative outcomes. Nutritional status, presence of dysphagia and dehydration were evaluated, as previously described.

Collected variables

Negative outcomes were defined as death and pulmonary complications after 6 months from admission. In the cohort of patients, death was related to cardiologic, urinary, haemorrhagic and thrombotic causes. As far as it is concerned the pneumologic complications, pneumonia was diagnosed as probable by the presence of (1) high fever (> 38°C), (2) 1 or more clinical symptoms or signs (for example purulent sputum), and (3) abnormal laboratory findings (leucocytosis or increased erythrocyte sedimentation rate or C-reactive protein level) and as definite when these 3 criteria were accompanied by lung infiltrates on chest radiography.

Statistical analysis

Survival analysis were performed with Kaplan-Meier curves (for mortality) and Cox's proportional hazard models (Hazard Ratio, 95% confidence interval, for pulmonary complications). First, log rank tests were used to test the difference in negative outcomes between patients with/without malnutrition, dysphagia, dehydration and CWL, Subsequently the interaction between CWL and malnutrition, dysphagia and dehydration and their impact on negative outcomes was analyzed in order to evaluate if the stratification of patients according to CWL affected survival.

4.3 Materials and methods of Phase 3

The aim of the third phase of the study was to perform a statistically-based exploratory analysis (using an unsupervised clustering method) in order to identify the presence of similar phenotypic subgroups of patients according to objective criteria. In addition, the ability of this classification system in predicting negative outcomes was also analyzed. The analysis was performed only in patients admitted to Acute care Unit since they were affected by the same disease. On the contrary, patients in Sub-acute care Unit were too heterogeneous.

Collected variables

Demographic information, medical comorbidities, medication usage, stroke related information and results of laboratory analyses were collected at admission in order to perform the exploratory analysis.

The dataset consisted of a total of 41 variables. This included 5 demographic variables (gender, age, weight, height, BMI), 6 stroke related variables (type of lesion, lesion location, presence of dysarthria, presence of aphasia, Barthel index, NIHSS), 8 nutrition related variables (FOIS, presence of enteral diet, length of enteral diet, MUST, presence of malnutrition, presence of CWL, percentage of weight loss, length of weight loss), 3 dysphagia related variables (presence of dysphagia, results of nurse screening, results of BSA), 19 laboratory related variables (hematocrit, albumin, total proteins, total cholesterol, LDL cholesterol, HDL cholesterol, sodium, potassium, glucose, urea, creatinine, BUN, BUN/Cr ratio, platelets, Vitamin b12, proteins in urine, urine gravity, homocysteine, folate). Prior to perform the cluster analysis the number of variables was reduced in order to analyze only those continuous variables known to be related to stroke and patient's characteristics, to the presence of dysphagia, malnutrition and dehydration.

Statistical analysis

In none of the 483 patients admitted to the Acute care Unit incomplete/missing data were reported. All the selected variables were used to define clusters. In order to do that, Ward's minimum-variance hierarchical method was used. The latter generates clusters by placing subjects into groups not defined a priori. Therefore, the subjects in one group tend to be similar to each other.

Once generated, the differences among the clusters for all the continuous and categorical variables (including those assessing the clinical outcomes) were analyzed using chi-square test and analysis of variance when appropriate. In addition, in order to evaluate the ability of this classification system in predicting negative outcomes, Kaplan-Meier curves (for mortality) and Cox's proportional hazard models (Hazard Ratio, 95% confidence interval, for pulmonary complications) were used to test differences in clinical outcomes among the clusters

CHAPTER 5: RESULTS

As the current project is structured into different phases, in this section, the results of the different phases are presented.

5.1 Results of Phase 1

A total of 686 patients were recruited, 483 of them were admitted to the Acute care Unit of our hospital, while the remaining 203 were admitted to the sub-acute care unit of our hospital. The results have been presented according to the patients' hospitalization.

- **Acute care Unit**

  A total of 483 patients admitted to the stroke unit of our hospital for acute ischemic stroke were consecutively enrolled. Among them, 240 were males and 243 were females. The mean age of the cohort was 75.5 ± 12.4 years (range 39-104 years). In the majority of the cases, the stroke was related to partial anterior circulation infarcts (n = 201). Information regarding the clinical characteristics of the enrolled population are reported in Table 5.1-1. Significant differences were found at Student t test between male and female patients for height and BMI, while no significant differences were found for weight, BI and NIHSS scores thus suggesting a similar stroke severity in males and females. A total of 108 patients, 39 males and 69 females were found aphasic, while dysarthria was found in 72 patients, 39 males and 33 females. These differences were found not significant on Chi-square test ($p = 0.145$ and $p = 0.322$ respectively). The same test did not reveal any significant difference in FOIS score between males and females patients.

  Dysphagia

  Dysphagia was suspected by nursing staff using the I-RBWH [88] in a total of 186 patients (38.5%), 72 males and 108 females. SLP or phoniatric evaluation confirmed the presence of dysphagia in 117 patients (24.2%), 57 males and 60 females. No difference in the prevalence of dysphagia between males and females was found on Chi-square test ($p = 0.899$). Mean age of dysphagic patients was 79.9 years, while mean age of non-dysphagic patients was 75.6 years. These differences were found significant on Student t test ($p = 0.048$). The prevalence at admission of malnutrition, dysphagia and dehydration is reported in Table 5.1.2.

Malnutrition

As far as it is concerned the prevalence of malnutrition at admission, according to the ESPEN diagnostic criteria for malnutrition, a total of 78 patients (16.2%), 33 males and 45 females were identified as malnourished. No differences in the prevalence of malnutrition between males and females were found on Chi-square comparison (p = 0.521). Mean age of malnourished patients was 81.4 years, while mean age of non malnourished patients was 74.5. These difference were found not significant on Student t test (p = 0.132). Malnutrition was found in 24 out of 117 patients with dysphagia and in 54 out of 366 patients without dysphagia. These differences were found not significant on Chi-square test (p = 0.454)

Dehydration

As far as it is concerned the hydration level of the enrolled patients, the BUN/Cr ratios obtained from the blood test performed at the admission was used. Under hydration was found in a total of 240 patients (49.7%), 93 males and 147 females. The difference in the prevalence of dehydration between males and females was found significant on Chi-square test (p = 0.007). The mean age of dehydrated patients was 77.1 years, while mean age of non-dehydrated patients was 74.1 years. These differences were found not significant on Student t test (p = 0.161). Dehydration was found in 63 out of 117 patients with dysphagia and in 177 out of 366 patients without dysphagia. These differences were found not significant on Chi-square test (p = 0.585).

Correlation among dysphagia, malnutrition and dehydration

No significant correlations were found on Phi test among malnutrition, dysphagia and dehydration. Significant correlations were demonstrated between presence of dysphagia and stroke severity (assessed through NIHSS); presence of dysphagia and stroke-related disability (assessed through BI); presence of dysphagia and ability con consume food (assessed through FOIS); and presence of dehydration and ability con consume food (assessed through FOIS) (see Table 5.1.3).

- **Sub-acute care Unit**

A total of 203 patients admitted to the Sub-acute care Unit were consecutively enrolled. Among them, 76 were males and 127 were females. The mean age of the cohort was 83.6 ± 6.8 years (range 63-98 years).

In the majority of the cases, the admission to the Sub-acute care Unit was related to cardiologic diseases (83 patients) or to infectious diseases (43 patients). Information regarding the clinical characteristics of the enrolled population are reported in Table 5.1-4. Significant differences were found at Student t test between male and female patients for weight, height and BMI. On the other hand, no significant differences in BI and FOIS scores between males and females patients was found. A total of 2 patients, 2 males and 0 females were found aphasic, while dysarthria was found in 4 patients, 2 males and 2 females. These differences were found not significant on Chi-square test ($p = 0.931$ and $p = 0.725$ respectively).

Dysphagia

A total of 45 patients (22.2%), 28 males and 17 females, were found dysphagic. A significant difference in the prevalence of dysphagia between males and females was found on Chi-square test ($p = 0.003$). Mean age of dysphagic patients was 83.5 years, while mean age of non-dysphagic patients was 83.9 years. These differences were found not significant on Student t test ($p = 0.924$). The mean BMI score in dysphagic patients was 22.6 kg/m^2 while the mean BMI score in non-dysphagic patients was 24.3 kg/m^2. These differences were found not significant on Student t test ($p = 0.207$). On the other hand, the BI scores obtained in dysphagic and non-dysphagic patients were significantly different. In particular, the BI mean score in dysphagic patients was 25.1, while in non-dysphagic patients it was 49.7 ($p = 0.001$). The Chi-square test demonstrated significant differences between dysphagic and non-dysphagic patients in the presence of malnutrition and in the functional oral intake ($p = 0.012$ and $p = 0.001$ respectively). On the other hand, no differences in the presence of dehydration in dysphagic and non-dysphagic patietns was demonstrated at chi-square test. The prevalence at admission of malnutrition, dysphagia and dehydration is reported in Table 5.1.5.

Malnutrition

As far as it is concerned the prevalence of malnutrition at admission, according to the ESPEN diagnostic criteria for malnutrition, a total of 44 patients (21.6%), 16 males and 28 females were identified as malnourished. No differences in the prevalence of malnutrition between males and females were found on Chi-square comparison ($p = 0.383$). Mean age of malnourished patients was 84.7 years, while mean age of non malnourished patients was 83.6. These difference were found not significant on Student t test ($p = 0.366$). The mean BMI score in malnourished patients was 18.5 kg/m^2 while the mean BMI score in non-malnourished patients was 25.5 kg/m^2. These differences were found significant on Student t test ($p = 0.001$). Malnutrition was found in 14 out of 45 patients with dysphagia and in 30 out of 158 patients without dysphagia. These differences were found significant on Chi-square test ($p = 0.046$)

Dehydration

Under hydration was found in a total of 93 patients (45.8%), 33 males and 60 females. The difference in the prevalence of dehydration between males and females was found not significant on Chi-square test ($p = 0.127$). The mean age of dehydrated patients was 83.2 years, while mean age of non-dehydrated patients was 85.3 years. These differences were found not significant on Student t test ($p = 0.363$). Dehydration was found in 30 out of 45 patients with dysphagia and in 63 out of 158 patients without dysphagia. These differences were found significant on Chi-square test ($p = 0.025$).

Correlation among dysphagia, malnutrition and dehydration

No significant correlations were found on Phi test among malnutrition, dysphagia and dehydration. Significant correlations were demonstrated between presence of dysphagia and BI and FOIS; and between presence of dehydration and FOIS) (see Table 5.1.6).

5.2 Results of Phase 2

The association among negative outcomes and malnutrition, dysphagia, dehydration and CWL was analyzed in both the 483 and 203 patients admitted to the Acute or Sub-acute care Units respectively. The results have been presented according to the patients' hospitalization.

- **Acute care Unit**

  Death

  Among the 483 patients enrolled in the Acute care Unit, 102 died. Thirty-six died during the hospitalization period (< 30 days), while the remaining 66 died during the follow-up period. The effect of malnutrition, dysphagia, dehydration and CWL on survival was assessed using the Kaplan-Meier curves with log rank test.

  - *Dysphagia:* a total of 117 patients were considered dysphagic at admission. Among them 42 died, 9 during hospitalization and the remaining 33 during the follow-up period. Kaplan-Meier with log rank test revealed a significant difference in the long term survival between patients with and without dysphagia. In particular, dysphagic patients died more frequently than those without dysphagia during the follow-up period ($p = 0.011$). On the other hand, no difference in the short term survival between patients with and without dysphagia was found (see figures 5.2-1 and 5.2-2).
  - *Malnutrition:* a total of 78 patients were malnourished ad admission. Among them 24 died, 9 during hospitalization and 15 during the follow-up period. No differences were found on log rank test in the distribution of death both in the short and long term periods between patients with/without malnutrition at admission ($p = 0.336$ and $p = 0.115$ respectively) (see figures 5.2-3 and 5.2-4).
  - *Dehydration:* a total of 240 patients were found dehydrated at admission. Among them 63 patients died, 21 during hospitalization and 42 during follow-up. Kaplan-Meier with log rank test did not reveal a significant difference both in the short or long term survival between patients with and without dehydration ($p = 0.554$ and $p = 0.126$ respectively) (see figures 5.2-5 and 5.2-6).
  - *CWL:* critical weight loss was found in 36 patients. Among them 18 died, 9 during hospitalization and 9 during follow-up. Kaplan-Meier with log rank revealed a significant effect of CWL on survival, both in

the short and in the long term period ($p = 0.008$ and $p = 0.001$ respectively) (see figures 5.2-7 and 5.2-8).

Since the CWL was the only clinical condition affecting both the short and long term survival a stratification was performed a priori according to the presence of CWL. The stratified analysis assessed the relative effect of dysphagia, malnutrition and dehydration according to the presence of CWL.

- *Effect of dysphagia stratified by CWL on long term survival:* among the 36 patients who experienced CWL, 12 were found dysphagic. Six of them died during the follow-up period (50%). Twelve out of the remaining 24 patients with CWL but without dysphagia died (50%). Among the 447 patients who did not experienced CWL, dysphagia significantly affect survival. Only 14% of patients without CWL and dysphagia died during the follow-up versus the 34.3% rate of death in patients with dysphagia and without CWL. This difference was found significant on Kaplan-Meier analysis ($p = 0.015$) (see figures 5.2-9 and 5.2-10).
- *Effect of dysphagia stratified by CWL on short term survival:* Kaplan-Meier analysis of survival did not found a significant effect of the stratification by CWL on short term survival for patients with/without dysphagia ($p = 0.990$).
- *Effect of malnutrition stratified by CWL on long term survival:* a total of 36 patients experienced CWL and were found malnourished. Among the remaining 447 patients who did not experienced CWL, a total of 42 were found malnourished. The survival curves obtained through Kaplan-Meier analysis revealed a significant effect of the combination of CWL and malnourishment on survival ($p = 0.002$). In particular, 18 out of 36 patients with CWL and malnourishment died during the follow-up, while only 6 out of 42 malnourished patients without CWL died during the follow-up.
- *Effect of malnutrition stratified by CWL on short term survival:* Kaplan-Meier analysis of survival did not found a significant effect of the stratification by CWL on short term survival for patients with/without malnutrition.

- *Effect of dehydration stratified by CWL on long term survival:* among the 36 patients who experienced CWL, 15 were found dehydrated. Nine of them died during the follow-up period (60%). Nine out of the remaining 21 patients with CWL but without dehydration died (42.9%). This difference was found significant on Kaplan-Meier analysis (p = 0.049). Also among the 447 patients who did not experienced CWL, dehydration affected survival significantly (see figures 5.2-11 and 5.2-12).
- *Effect of dehydration stratified by CWL on short term survival:* Kaplan-Meier analysis of survival did not found a significant effect of the stratification by CWL on short term survival for patients with/without dehydration.

Pulmonary complications

Among the 483 patients enrolled in the Acute care Unit, a total of 36 patients developed pulmonary complications, 6 during hospitalization and 30 during the follow-up period. All the patients who developed pulmonary complications during hospitalization died and 21 out of 30 patients who developed pulmonary complication during the follow-up period died. The presence of pulmonary complication affected significantly survival both in the short and in the long term periods (p = 0.015 and p = 0.032 on chi-square test). The Cox regression analysis was used to evaluate the risk to develop pulmonary complications according to the presence of malnutrition, dysphagia, dehydration and CWL.

- *Malnutrition:* the presence of malnutrition did not affect the risk to develop pulmonary complication both in the short and in the long term period (OR = 1.127; p = 0.805 and OR = 1.370; p = 0.691 respectively).
- *Dysphagia:* the presence of dysphagia increased the risk to develop pulmonary complications both in the long term period (OR = 6.236; p = 0.004), and in the short term period (OR = 5.493; p = 0.007). The survival function at mean of covariates indicating the cumulative survival during the follow-up period depending by death for pulmonary complications and according to the presence of dysphagia is reported in figure 5.2-13.

- *Dehydration:* Cox regression analysis did not revealed a significant effect of hydratation level on the risk of develop pulmonary complication in the short and in the long term period (OR = 2.213; p = 0.098; OR = 1.480; p = 0.426).
- *CWL:* the presence of CWL affected significantly the risk of develop pulmonary complications during both the short and long term period (OR = 2.971; p = 0.048; OR = 4.588; p = 0.049). The survival function at mean of covariates indicating the cumulative survival during the follow-up period depending by death for pulmonary complications and according to the presence of CWL is reported in figure 5.2-14.

- **Sub-acute care Unit**

  Death

  Among the 203 patients enrolled in the Sub-Acute care Unit, 12 died during the follow-up period. The effect of malnutrition, dysphagia, dehydration and CWL on survival was assessed using the Kaplan-Meier curves with log rank test.

  - *Dysphagia:* a total of 45 patients were considered dysphagic at admission. Among them 8 died during the follow-up period. Kaplan-Meier with log rank test revealed a significant difference in the long term survival between patients with and without dysphagia. In particular, dysphagic patients died more frequently than those without dysphagia during the follow-up period (p = 0.001) (see figures 5.2-15).
  - *Malnutrition:* a total of 44 patients were malnourished ad admission. Among them 4 died during the follow-up period. No differences were found on log rank test in the distribution of death between patients with/without malnutrition at admission (p = 0.314) (see figures 5.2-16).
  - *Dehydration:* a total of 93 patients were found dehydrated at admission. Among them 7 patients died during follow-up. Kaplan-Meier with log rank test did not reveal a significant difference in survival between patients with and without dehydration (p = 0.544).

- *CWL:* critical weight loss was found in 38 patients. Among them 6 died during follow-up. Kaplan-Meier with log rank revealed a significant effect of CWL on survival (p = 0.004) (see figures 5.2-17).

Also in Sub-acute care setting a a priori stratification according to the presence of CWL was performed in order to evaluate the relative effect of dysphagia, malnutrition and dehydration according to the presence of CWL.

- *Effect of dysphagia stratified by CWL on survival:* among the 38 patients who experienced CWL, 16 were found dysphagic. Six of them died during the follow-up period (37.5%). Zero out of the remaining 22 patients with CWL but without dysphagia died (0%). This difference was found significant on log-rank (p = 0.006). On the other hand, among the 165 patients who did not experienced CWL, dysphagia did not significantly affect survival (see figures 5.2-18 and 5.2-19).
- *Effect of malnutrition stratified by CWL on survival:* the survival curves obtained through Kaplan-Meier analysis did not revealed a significant effect of the combination of CWL and malnourishment on survival (p = 0.832).
- *Effect of dehydration stratified by CWL on survival:* also in this case, the survival curves obtained through Kaplan-Meier analysis did not revealed a significant effect of the combination of CWL and dehydration on survival (p = 0.422).

Pulmonary complications

Among the 203 patients enrolled in the Sub-acute care Unit, a total of 18 patients developed pulmonary complications during the follow-up period and 8 died. The presence of pulmonary complication affected significantly survival (p = 0.003 on chi-square test). The Cox regression analysis was used to evaluate the risk to develop pulmonary complications according to the presence of malnutrition, dysphagia, dehydration and CWL.

- *Dysphagia:* the presence of dysphagia increased the risk to develop pulmonary complications (OR = 2.809; p = 0.029).
- *Malnutrition:* the presence of malnutrition did not affect the risk to develop pulmonary complication (OR = 1.807; p = 0.239).

- *Dehydration:* also in this case Cox regression analysis did not revealed a significant effect of hydratation level on the risk of develop pulmonary complication (OR = 1.719; p = 0.284).
- *CWL:* on the other hand, the presence of CWL affected significantly the risk of develop pulmonary complications (OR = 3.474; p = 0.009).

5.3 Results of Phase 3

21 and the differences across the 4 clusters are presented in table 5.3-1 (for continuous variables) and 5.3-2 (for categorical variables).

- **Cluster 1**

  Cluster 1 was composed by 18 patients (4.7%). This cluster was characterized by the highest BMI (27.1 kg/m^2), Barthel Index (60.2), triglycerides (356.2 mg/dL), folate (10.2 ng/mL), and the lowest cholesterol HDL (39.2 mg/dL), Vitamin B12 levels (330.0 pg/mL), and BUN/Cr ratio (14.7). Patients in this cluster were more frequently males (66.7%) and were more frequently affected by dysphagia (33.4%)
- **Cluster 2**

  Cluster 2 was composed by 117 patients (24.2%). This cluster was characterized by highest age (78.7 years), platelets (283.1 x 10^9/L), Vitamin B12 levels (508.9 pg/mL), and BUN/Cr ratio (24.6), lowest weight (64.2 kg), BMI (20.3 kg/m^2), Barthel Index (28.9), Albumin levels (2.9 g/dL), glucose level (97.7 mg/dL), total proteins (6.1 g/dL), cholesterol total (163.8 mg/dL), cholesterol LDL (93.9 mg/dL), triglycerides (89.5 mg/dL). Patients in cluster 2 were more frequently females (82.1%), malnourished (35.9%), dehydrated (53.8%), and were more frequently affected by CWL (23.1%).
- **Cluster 3**

  Cluster 3 was composed by a total of 222 patients (46%). Cluster 3 was characterized by lowest values of creatinine (0.94 mg/dL), homocysteine (16.9 micromol/L), and platelets (166.5 x 10^9/L), and highest values of cholesterol LDL (154.1 mg/dL) and sodium (139.4 mmpl/L).
- **Cluster 4**

  Cluster 4 was composed by 126 patients (25.1%). This cluster was characterized by highest values of glucose (113.5 mg/dL), cholesterol total (235.2 mg/dL), cholesterol LDL (154.1 mg/dL), and lowest values of folate

(6.1 ng/mL). In none of the patients of Cluster 4 a CWL was detected. Dysphagia was significantly less frequent in patients of Cluster 4.

Once the clusters were defined the negative outcomes according to the clusters were assessed. Death both in short and in long term periods was significantly more common in Cluster 2 patients. In particular, among the 36 patients who died during hospitalization, 21 were grouped in Cluster 2 and 15 in Cluster 3. None of the patients of Cluster 1 and 4 died during the hospitalization period. These differences were found significant on Chi-square analysis (p = 0.019). In particular, death during hospitalization occurred significantly more frequently in Cluster 2 patients (17.9%) than in Cluster 3 (6.8%), Cluster 1 (0%) or Cluster 4 (0%). Death during the follow-up period occurred in 66 patients, 24 of them (20.5%) were grouped in Cluster 2, 24 patients (10.8%) were grouped in Cluster 3, 3 patients (16.6%) were grouped in Cluster 1, and 15 patients (11.9%) were grouped in Cluster 4. These differences were found significant on chi-square test (p =0.037). In particular, death during the follow-up up period seem to occur significantly more frequently in Cluster 2 patients.

As far as it is concerned the pulmonary complication, a total of 36 patients developed pulmonary complications during hospitalization or during the follow-up period. No differences in the distribution of pulmonary complications among the 4 cluster during hospitalization (6 cases) was demonstrated on chi-square test (p = 0.112). On the contrary, among the 30 patients who developed pulmonary complications during the follow-up period, 7 of them were grouped in Cluster 1. These differences were found significant on chi-square test (p = 0.021).

CHAPTER 6: DISCUSSION

Phase 1

In the present study the prevalence at admission and the relationships among malnutrition, dysphagia and dehydration in a group of 686 patients admitted to the Acute and Sub-acute care Units were analyzed.

Patients admitted to the Acute care Unit were affected by acute ischemic stroke. In this cohort malnutrition was found in 16.2% of patients at admission. This datum appears lower than those reported by Crary et al [182], who analyzed the nutritional status and presence of dysphagia at admission in a group of 76 patients with acute ischemic stroke, and found poor nutritional status in 26.3% of patients. Poels et al [183] who analyzed a group of 69 patients admitted to rehabilitation unit after an acute stroke reported a malnutrition prevalence of 35%. Also Westergren et al [184] reported a malnutrition prevalence of 32% in a group of 162 patients admitted to a stroke rehabilitation unit. On the other hand, Davalos et al [9] found malnutrition in 16.3% of a group of 104 patients admitted to hospital with an acute stroke; while Chai et al [185] found a malnutrition prevalence of 8.2% in a group of 61 patients admitted to infirmary with significant disability following stroke. It is possible that these differences could be related to the instrument used to assess malnutrition and to the timing of assessment. In particular, Crary et al [182] used the Mini Nutritional Assessment (MNA). The latter includes anthropomorphic measures (such as BMI) and information regarding dietary changes, weight loss, and stress factors that may have occurred 3 months before the evaluation. Westergren et al [184] used a modified version of the Subjective Global Assessment. Poels et al [183] evaluated the presence of malnutrition at admission in rehabilitation service (which occurred 34 day after the stroke). On the other hand, in the present study malnutrition was assessed at admission and defined according to the consensus-based minimum set of malnutrition criteria proposed in 2015 by the European Society for Clinical Nutrition and Metabolism [170].

As far as it is concerned the swallowing impairment, the 24.2% of patients were considered dysphagic at admission. This results appear lower than those previously reported. In particular, in the international literature, the estimated incidence of post-stroke dysphagia ranges between 19% and 81% of acute stroke survivors [22]. Crary et al [11] reported a prevalence of dysphagia of 37% in a group of 67 patients with ischemic stroke. In Davalos et al study [9] the prevalence of dysphagia was 30%; in Westergren et al al study [184] dysphagia affected 25% of patients. Also Martineau et al [186] found dysphagia in 40% of a group of 73 patients admitted to stroke unit for an acute stroke. It is possible that these

diverging results are related to the diagnostic criteria used to identify this condition. In particular, in our study patients were considered dysphagic only after BSA and/or FEES examination performed in the Phoniatric Unit of our hospital. It is consequently possible that the use of more rigorous criteria for the diagnosis of dysphagia, may have reduced the prevalence of dysphagia at admission. Similar to previous reports [11, 182], also in the present study the presence of dysphagia was significantly associated with stroke severity.
Based on a BUN/Cr level > 20:1, the prevalence of dehydratation at admission was 49.7%. This datum appears very similar to the findings of Crary et al [11], who reported a prevalence of dehydration of 53%. Furthermore, dehydration was associated with oral intake (measured with FOIS) but not with stroke severity or presence of dysphagia. This is not in accordance with the findings of Crary et al [11], who demonstrated a significant association between dehydration and presence of dysphagia. However, in the study of Crary et al [11] only 67 patients were studied, in addition, and given the complexity of these univariate associations, it is difficult to speculate about specific factors that contribute to dehydration in acute ischemic stroke [11].
Interestingly, no significant association among malnutrition, dysphagia and dehydration were found at the time of hospital admission, thus suggesting that these three conditions, even if prevalent in patients with acute ischemic stroke, may co-exist independently before or immediately after stroke. This datum is not in accordance with those reported by Foley et al [13], who, in a systematic review concluded that the odds of malnutrition were increased if dysphagia was present following stroke. However, only five of the eight studies included in the review reported significant associations between dysphagia and malnutrition, and the pooled analysis revealed a significant effect only for trials conducted several weeks following stroke [11]. In addition, also Crary et al [11, 182] reported that nutritional measures did not correlate with dysphagia at admission. Moreover, also Davalos et al [9] did not found any nutritional differences between patients with and without swallowing problems at admission. It is consequently possible to speculate that the neurological damage may lead to an impairment of deglutition abilities that may limits the safely ingest of adequate amounts of food and/or liquid, but that this effect is not immediate.
As far as it is concerned the Sub-acute care Unit, dysphagia was reported in 22.2% of cases. Dysphagia was significantly more common in males than in females. The presence of swallowing disorders was significantly associated with the patient's functional status activity (measured through Barthel Index), while no significant association with the presence of malnutrition and dehydration was found. Also

malnutrition and dehydration were highly prevalent in patients admitted to the Sub-Acute care Unit with a prevalence of 22.2% and 45.8%.

These results appear very difficult to compare since to the best of our knowledge no previous study reported the prevalence of dysphagia, malnutrition and dehydration in Sub-acute care settings. These units admit heterogeneous groups of patients with acute illness, injury or exacerbation of a disease process who needed treatment for one or more specific active complex medical conditions or needed the administration of one or more technically complex treatments, in the context of a person's underlying long-term condition and overall situation. Previous studies focusing on hospitalized elderly patients reported quite different prevalence rates of dysphagia, malnutrition and dehydration. In particular, Roy et al [187] who analyzed a group of 65–94-year-old community dwelling adults, reported a prevalence of dysphagia of 37.6%. Serra-Prat et al [188] reported a prevalence of malnutrition of 18.6% among independently living older persons. Poisson et al [189] found dysphagia in 34 out of 159 and malnourishment in 77 out of 159 consecutive hospitalized elderly patients. On the other hand, Stricher et al [190] who analyzed data from 926 nursing homes units reported a dysphagia prevalence of 13.4% among a total of 23,549 residents and a dysphagia prevalence of 24% among the residents of nursing homes in Italy.

Phase 2

In the second phase of the study the association between malnutrition, dysphagia and dehydration at admission and short and long-term outcomes in hospitalized patients both in Acute and Sub-acute care settings was studied. In addition, since previous studies demonstrated that CWL leads to higher mortality risk, also this datum was analyzed. To the best of our knowledge this is the first study that investigates the association between dysphagia, malnutrition and dehydration and negative outcomes, stratified by the presence of CWL.

As far as it is concerned the survival, a total of 102 patients admitted to the Acute care Unit died, 36 during the hospitalization period and 66 during the follow-up period. In the Sub-acute care Unit, a total of 12 patients died during the follow-up period. No significant association between malnutrition and dehydration and mortality both in the short and in the long term periods was demonstrated in Acute or Sub-acute care settings. Also Davis et al [191] who analyzed the impact of undernutrition on stroke outcomes did not found a statistically significant association between the two variables. On the, other hand, in a recent study performed by the FOOD Trial

Collaboration [10], the authors reported that nutritional status early after stroke is independently associated with long-term outcome. It is possible that these diverging results could be related to the method used to assess malnutrition. In the FOOD Trial Collaboration study [10], in fact, the nutritional status was assessed by clinicians according to their own bedside assessment or, when practical, from a fuller assessment that might include weight, height, dietary history, or blood tests. In the present study, the presence of malnutrition was checked using always the same method.

Dysphagia significantly affected survival. In the Acute care Unit 33 out of the 117 patients with dysphagia died during the 6 months follow-up; while in the Sub-acute care Unit 8 out of the 45 patients with dysphagia died during the 6 months follow-up. This finding is in accordance with those reported by Arnold et al [192] who studied a total of 570 consecutive patients treated in a tertiary stroke center and found that dysphagic patients had less often a favourable outcome than non dysphagic patients (death in 13.6% vs. 1.6%). This finding is probably related to the higher risk of developing pulmonary complication in dysphagic patients (OR = 5.493; p = 0.007 in Acute care settings and OR = 2.809; p = 0.029 in Sub-acute care settings). In our sample pneumonia significantly affected survival. In the Acute care Unit 27 out of the 36 patients who developed pulmonary complication during the hospitalization and follow-up period, died. In the Sub-acute care Unit 8 out of the 18 patients who developed pulmonary complications during the follow-up period, died. The significant association between dysphagia and pneumonia is in accordance with previous reports. In particular Arnold et al [192] found that dysphagic patients suffered more frequently from pneumonia than non dysphagic patients (23.1% vs. 1.1%).

Critical weight loss significantly affected survival and increased the risk of develop pulmonary complications both in Acute and in Sub-acute care settings. These findings are in accordance with previous reports. In particular Newman et al. [175] reported that weight loss increased the risk of death in older adults (Hazard Ratio = 1.66); Wijnhoven et al. [193] found a significant association between mortality risk and unintentional weight loss due to medical reason in community-dwelling older adults (Hazard Ratio = 2.43). Also Allison et al [194] reported a significant association between weight and mortality rate. Finally, de van der Schueren et al [181] demonstrated that patients with CQL have a higher one-year mortality compared to patients with no critical weight loss. Interestingly, in this study a higher mortality risk was observed in patients with CWL and dysphagia than in patients with CWL and without dysphagia or in patients with dysphagia and without CWL (OR = 4.943; p = 0.019 in Acute care settings and OR = 2.732; p = 0.032 in Sub-acute care settings). It is possible that these two conditions may play a synergic role in the occurrence of negative outcomes in hospitalized patients.

Phase 3

In the third phase of the project a statistically-based exploratory analysis was performed using an unsupervised clustering method in order to identify the presence of similar phenotypic subgroups of patients according to objective criteria. Only continuous variables known or suspected to be associated with the severity of stroke, the patient's characteristics and the presence of dysphagia, malnutrition and dehydration were used in this analysis.

In the clinical practice, acute stroke survivors are mainly classified according to the severity and location of the stroke even if some authors [13, 171, 173, 178-181, 188, 191-191] pointed out the importance of other variables (such as weight loss, malnutrition and dysphagia) in determining the occurrence of negative outcome. However, the impact of these parameters are still a subject of debate and it appear not advisable to classify patients with stroke according only to the presence of a combination of these parameters. In the present study, rather than using a priori defined characteristics, we used unsupervised statistical methods to generate clusters based on prospectively collected clinical data from a large cohort of patients admitted to the Acute care Unit. Interestingly, traditional measures such as the severity of stroke, length of enteral diet, presence of dysarthria, presence of aphasia, use of diuretic drugs and oral intake did not differ significantly across clusters. On the contrary, measures such as age, BMI, barthel index scores, hematocrit, serum glucose, total proteins, BUN/Cr ratio, platelets number and albumin, cholesterols, triglycerides, folate, homocysteine levels, characterized differences between groups.

It must be noted that the identified clusters simply describe patients which share common clinical features and it is unlikely that these clusters represent distinct pathophysiologies of acute stroke. Nonetheless, regardless of underlying pathophysiology, patients in different clusters have different prognoses. In particular, patients in Cluster 2 have the poorest prognosis and were characterized by CWL, dehydration, highest age, malnutrition, low BMI, low albumin level, low proteins level.

On the other hand, patients in cluster 1 were more frequently affected by dysphagia and developed pulmonary complications more frequently.
To the best of our knowledge, clustering techniques have never been applied in acute stroke survivors. However, the results here reported might be useful in clinical practice because if discrete meaningful differences exist among acute stroke survivors, then these differences could be used to objectively classify patients in order to improve prognostication and guide patient decision-making.

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TABLES

Phase 1: Acute care Unit

Table 5.1.1: clinical characteristics of the patients admitted to the Acute care Unit. The results of the comparison through Student t test are also reported. In bold statistically significant comparisons. BMI = body mass index; NIHSS = NIH stroke scale.

	Males (n = 240)	**Females (n = 243)**	**p**	**Total (n = 483)**
Weight	74.6 ± 11.2 kg (48-96 kg)	66.8 ± 13.1 kg (38-110 kg)	0.562	70.5 ± 12.7 kg (38-110 kg)
Height	1.71 ± 0.06 m (1.57-1.85 m)	1.61 ± 0.07 m (1.40-1.75 m)	**0.004**	1.66 ± 0.08 m (1.40-1.85 m)
BMI	25.3 ± 3.1 kg/m^2 (17.3-32.5 kg/m^2)	25.8 ± 5.3 kg/m^2 (14.8-43 kg/m^2)	**0.003**	25.5 ± 4.3 kg/m^2 (14.8-42.9 kg/m^2)
Bartel index	42.7 ± 31.2 (0-100)	35.3 ± 26.7 (0-100)	0.160	39.1 ± 29.1 (0-100)
NIHSS	6.2 ± 6.1 (0-25)	7.6 ± 6.6 (0-27)	0.352	6.9 ± 6.4 (0-27)

Table 5.1.2: Prevalence of malnutrition, dysphagia and dehydration at admission in Acute care Unit. The results of comparison through Chi-square test are also reported. Percentage are reported in bracketes. In bold statistically significant comparisons.

	Males (n = 240)	**Females (n = 243)**	**p**	**Total (n = 483)**
Malnutrition	33/240 (13.8%)	45/243 (18.5%)	0.521	78/483 (16.2%)
Dysphagia	57/240 (23.8%)	60/243 (24.7%)	0.899	117/483 (24.2%)
Dehydration	93/240 (38.8%)	147/243 (60.5%)	**0.007**	240/483 (49.7%)

Table 5.1.3: correlations among malnutrition, dysphagia and dehydration assessed through Phi test. FOIS = functional oral intake, BI = barthel index; NIHSS = NIH stroke severity.

** = p < 0.001

	Malnutrition	**Dysphagia**	**Dehydration**	**FOIS**	**BI**	**NIHSS**
Malnutrition	1	0.134	0.221	-0.104	-0.076	-0.059
Dysphagia	0.134	1	0.178	-0.588**	0.178	0.307**
Dehydration	0.221	0.178	1	-0.288**	-0034	0.154
FOIS	-0.104	-0.588**	-0.288**	1	0.252**	-0.528**
BI	-0.076	-0.225**	-0.034	0.252**	1	-0.216**
NIHSS	-0.059	0.307**	0.154	-0.528**	-0.216**	1

Phase 1: Sub-acute care Unit

Table 5.1.4: clinical characteristics of the enrolled patients. The results of the comparison through Student t test are also reported. In bold statistically significant comparisons. BMI = body mass index.

	Males (n = 76)	**Females (n = 127)**	**p**	**Total (n = 203)**
Weight	66.3 ± 12.1 kg (39-93 kg)	62.9 ± 20.6 kg (36-163 kg)	**0.019**	64.2 ± 18.7 kg (36-163 kg)
Height	1.68 ± 0.22 m (1.74-1.84 m)	1.52 ± 0.20 m (1.58-1.75 m)	**0.024**	1.58 ± 0.25 m (1.58-1.84 m)
BMI	23.3 ± 4.4 kg/m^2 (13.7-35.2 kg/m^2)	24.3 ± 5.3 kg/m^2 (11.8-42.5 kg/m^2)	**0.007**	23.9 ± 5.1 kg/m^2 (11.8-42.5 kg/m^2)
Bartel index	38.3 ± 28.9 (0-99)	47.9 ± 30.7 (0-100)	0.537	44.3 ± 30.2 (0-100)

Table 5.1.5: Prevalence of malnutrition, dysphagia and dehydration in patients enrolled in the Sub-acute care Unit. The results of comparison through Chi-square test are also reported. Percentage are reported in bracketes. In bold statistically significant comparisons.

	Males (n = 76)	**Females (n = 127)**	**p**	**Total (n = 203)**
Malnutrition	16/76 (21.1%)	28/127 (22%)	0.383	44/203 (22.2%)
Dysphagia	28/76 (36.8%)	17/127 (13.4%)	**0.003**	45/203 (22.2%)
Dehydration	33/76 (43.4%)	60/127 (47.2%)	0.363	93/203 (45.8%)

Table 5.1.6: correlations among malnutrition, dysphagia and dehydration assessed through Phi test in Sub-acute care Unit patients. FOIS = functional oral intake, BI = barthel index; NIHSS = NIH stroke severity.

	Malnutrition	**Dysphagia**	**Dehydration**	**FOIS**	**BI**
Malnutrition	1	0.097	0.203	0.112	0.074
Dysphagia	0.097	1	0.378*	-0.716**	-0.217*
Dehydration	0.203	0.378*	1	-0.318**	0.134
FOIS	-0.104	-0.716**	-0.318**	1	0.202**
BI	-0.076	-0.217*	0.134	0.202**	1

* = $p < 0.05$

** = $p < 0.01$

Phase 2: Acute care Unit

Figure 5.2-1: Kaplan-Meier analysis of survival according to dysphagia during the follow-up period (6 months) in the 483 patients admitted to the Acute care Unit. A total of 102 patients died, 36 during hospitalization and 66 during the follow-up period.

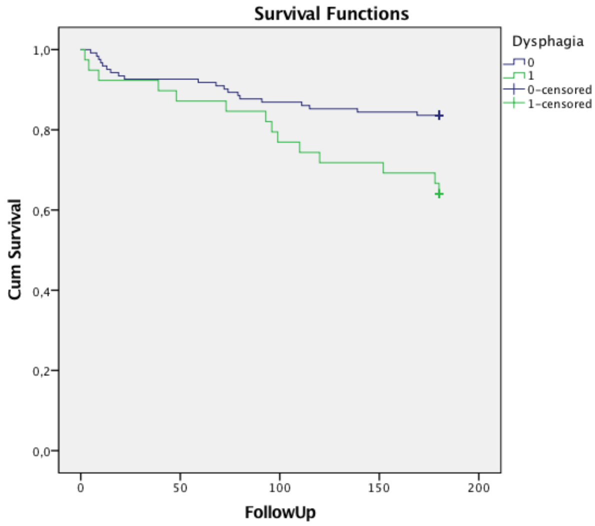


Figure 5.2-2: Kaplan-Meier analysis of survival according to dysphagia during the hospitalization (30 days) in the 483 patients admitted to the Acute care Unit. A total of 102 patients died, 36 during hospitalization and 66 during the follow-up period.

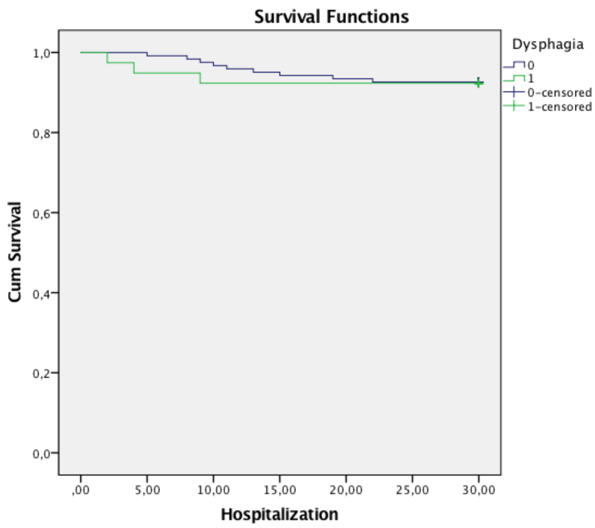


Figure 5.2-3: Kaplan-Meier analysis of survival according to nutritional status during the follow-up period (6 months) in the 483 patients admitted to the Acute care Unit. A total of 102 patients died, 36 during hospitalization and 66 during the follow-up period.

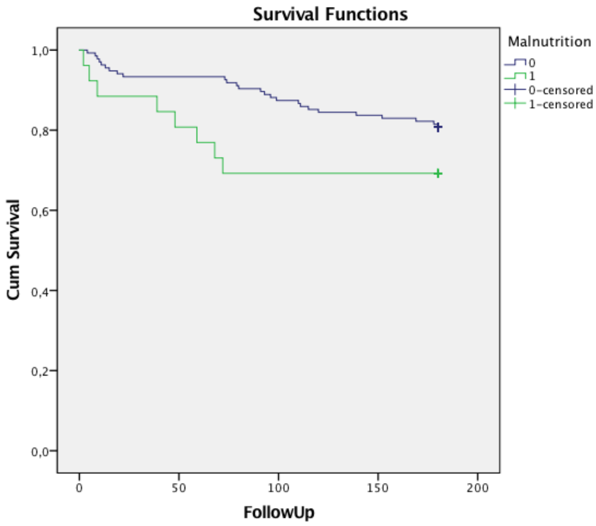


Figure 5.2-4: Kaplan-Meier analysis of survival according to nutritional status during the hospitalization (30 days) in the 483 patients admitted to the Acute care Unit. A total of 102 patients died, 36 during hospitalization and 66 during the follow-up period.

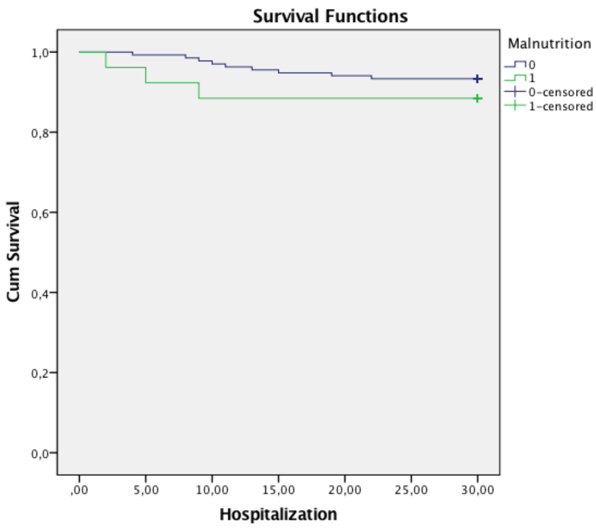


Figure 5.2-5: Kaplan-Meier analysis of survival according to hydratation level during the follow-up period (6 months) in the 483 patients admitted to the Acute care Unit. A total of 102 patients died, 36 during hospitalization and 66 during the follow-up period.

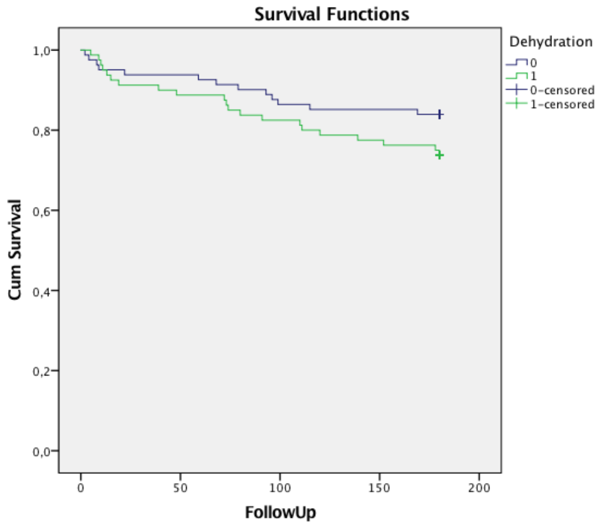


Figure 5.2-6: Kaplan-Meier analysis of survival according to hydratation level during the hospitalization (30 days) in the 483 patients admitted to the Acute care Unit. A total of 102 patients died, 36 during hospitalization and 66 during the follow-up period.

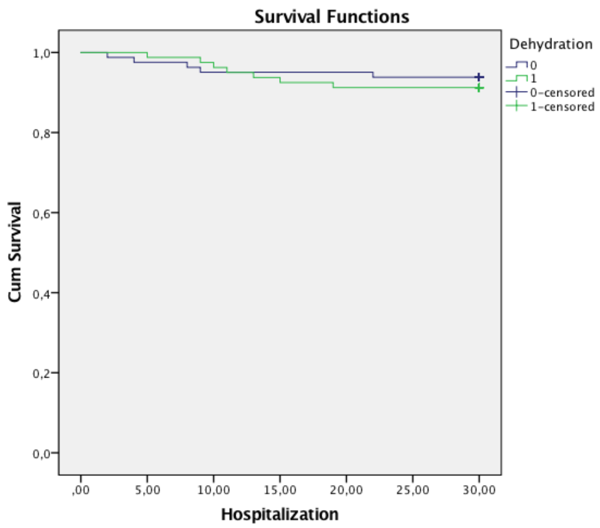


Figure 5.2-7: Kaplan-Meier analysis of survival according to CWL during the follow-up period (6 months) in the 483 patients admitted to the Acute care Unit. A total of 102 patients died, 36 during hospitalization and 66 during the follow-up period.

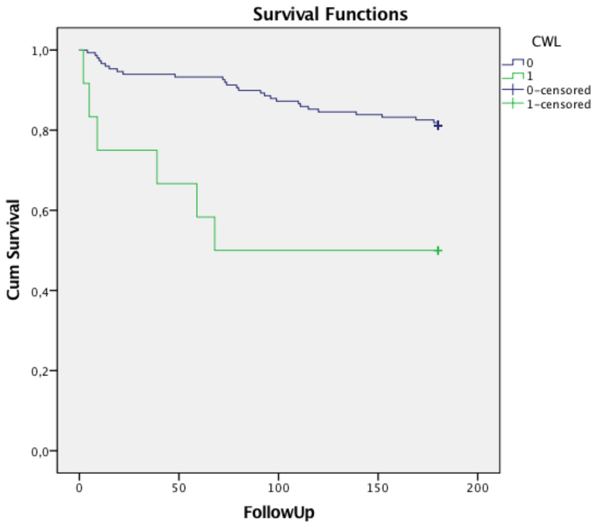


Figure 5.2-8: Kaplan-Meier analysis of survival according to CWL during the hospitalization (30 days) in the 483 patients admitted to the Acute care Unit. A total of 102 patients died, 36 during hospitalization and 66 during the follow-up period.

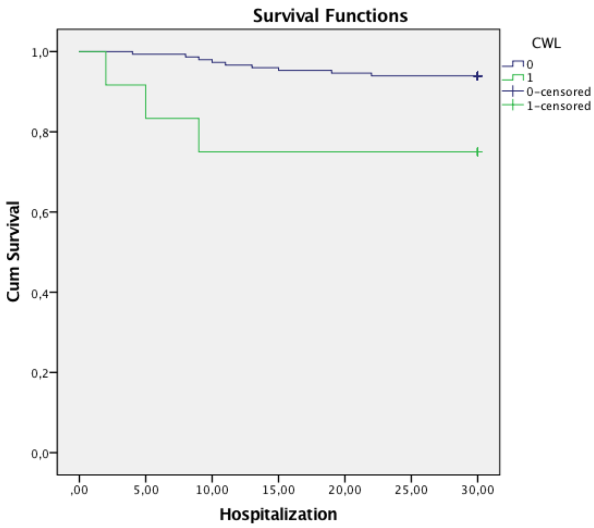


Figure 5.2-9: Kaplan-Meier analysis of survival in patients who did not experienced CWL (CWL = 0) (n = 447) according to the presence of dysphagia (6 months).

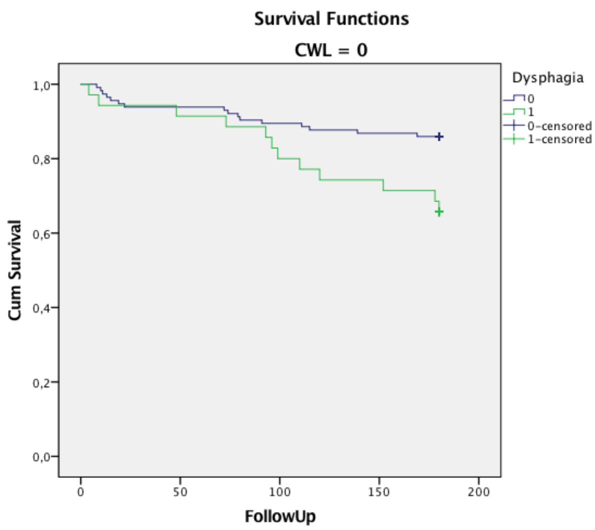


Figure 5.2-10: Kaplan-Meier analysis of survival in patients who experienced CWL (CWL = 1) (n = 36) according to the presence of dysphagia (6 months).

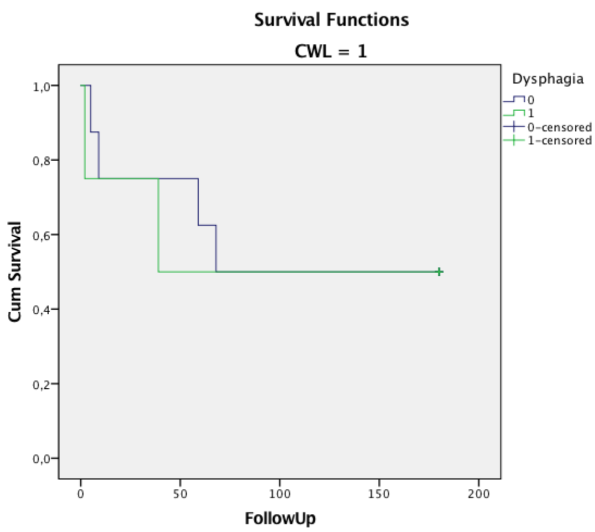


Figure 5.2-11: Kaplan-Meier analysis of survival in patients who did not experienced CWL (CWL = 0) (n = 447) according to the presence of dehydration (6 months).

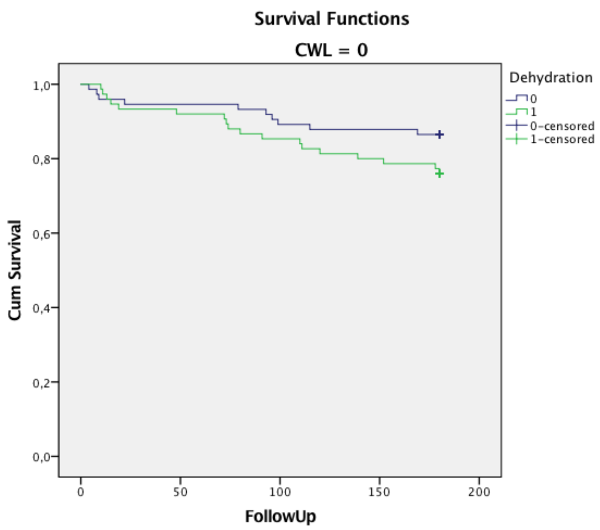


Figure 5.2-12: Kaplan-Meier analysis of survival in patients who experienced CWL (CWL = 1) (n = 36) according to the presence of dehydration (6 months).

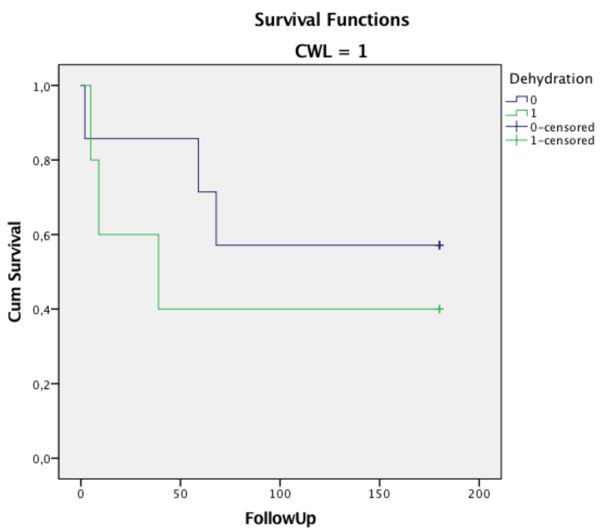


Figure 5.2-13: Cumulative survival during the follow-up period depending by death for pulmonary complications and according to the presence of dysphagia.

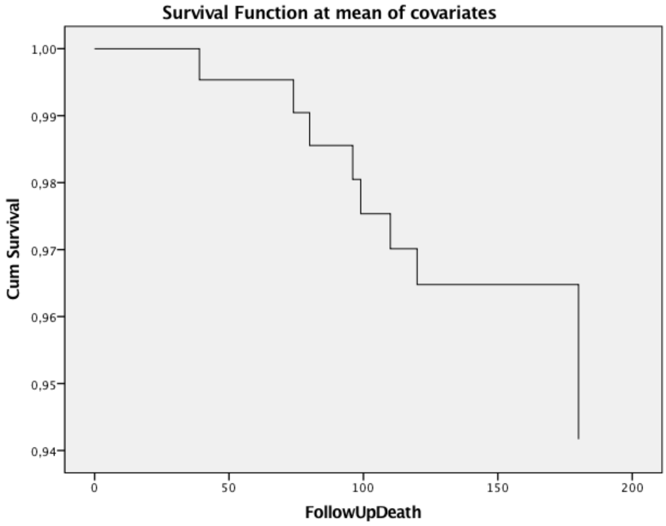
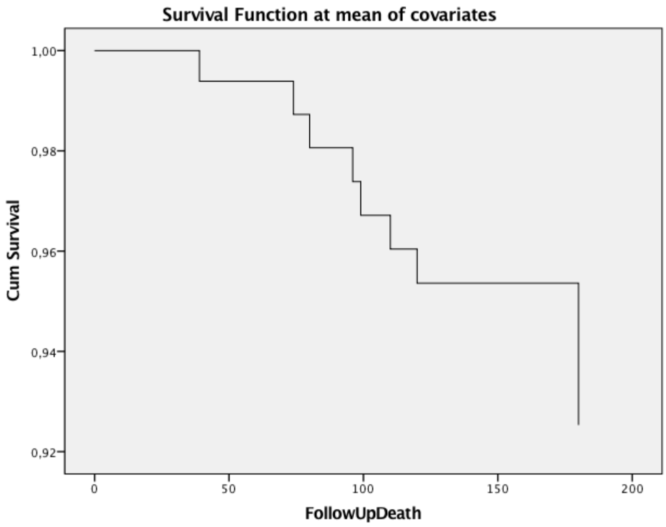


Figure 5.2-14: Cumulative survival during the follow-up period depending by death for pulmonary complications and according to the presence of CWL.



Phase 2: Sub-acute care Unit

Figure 5.2-15: Kaplan-Meier analysis of survival according to dysphagia during the follow-up period (6 months) in the 203 patients admitted to the Sub-acute care Unit. A total of 12 patients died during the follow-up period.

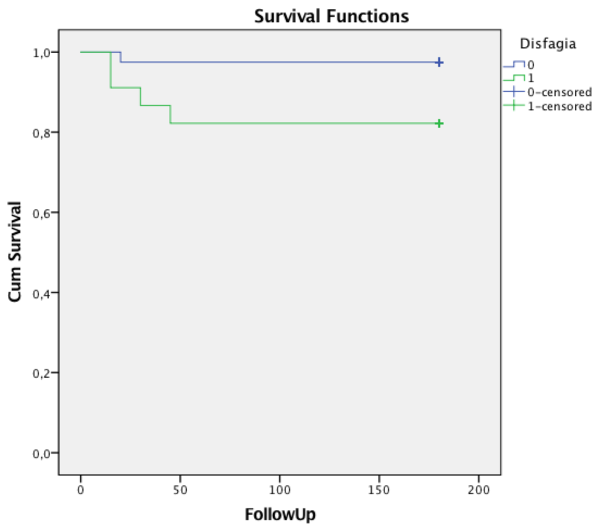


Figure 5.2-16: Kaplan-Meier analysis of survival according to malnutrition during the follow-up period (6 months) in the 203 patients admitted to the Sub-acute care Unit. A total of 12 patients died during the follow-up period.

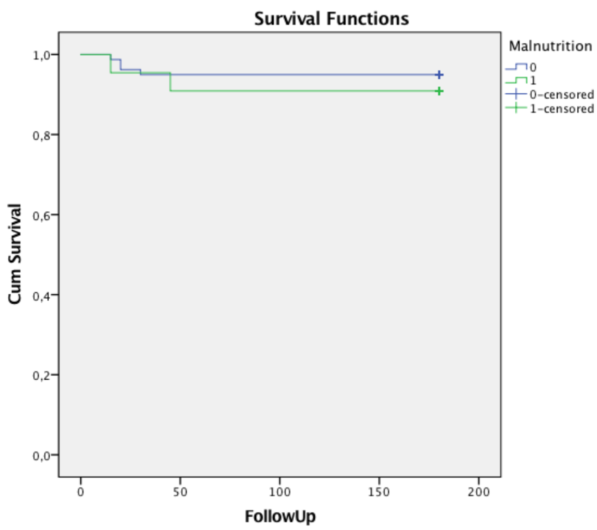


Figure 5.2-17: Kaplan-Meier analysis of survival according to CWL during the follow-up period (6 months) in the 203 patients admitted to the Sub-acute care Unit. A total of 12 patients died during the follow-up period.

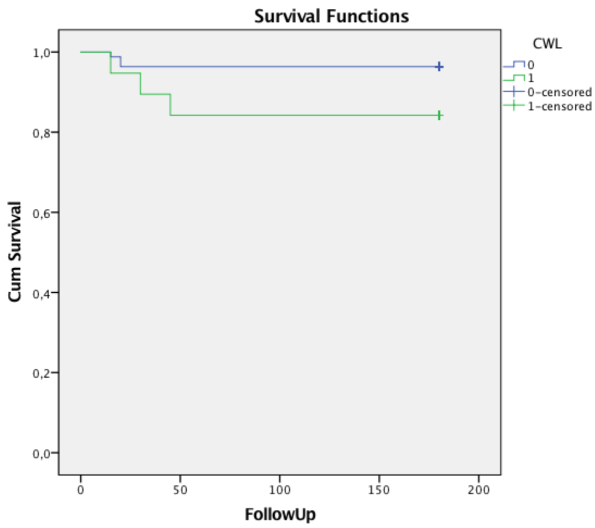


Figure 5.2-18: Kaplan-Meier analysis of survival in patients who did not experienced CWL (CWL = 0) (n = 165) according to the presence of dysphagia (6 months) in the 203 patients admitted to the Sub-acute care Unit. A total of 12 patients died during the follow-up period.

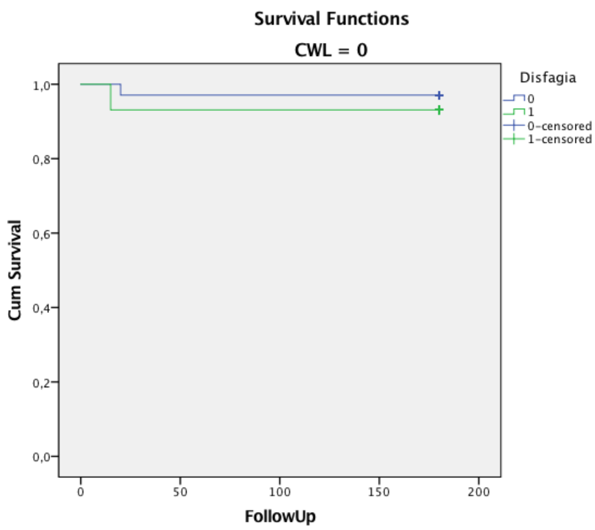
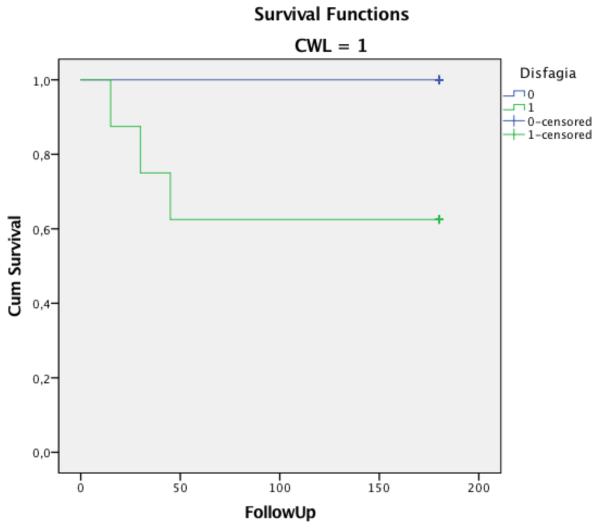


Figure 5.2-19: Kaplan-Meier analysis of survival in patients who experienced CWL (CWL = 1) (n = 38) according to the presence of dysphagia (6 months) in the 203 patients admitted to the Sub-acute care Unit. A total of 12 patients died during the follow-up period.



Phase 3

Figure 5.3-1: Dendrogram for development of 4 clusters.

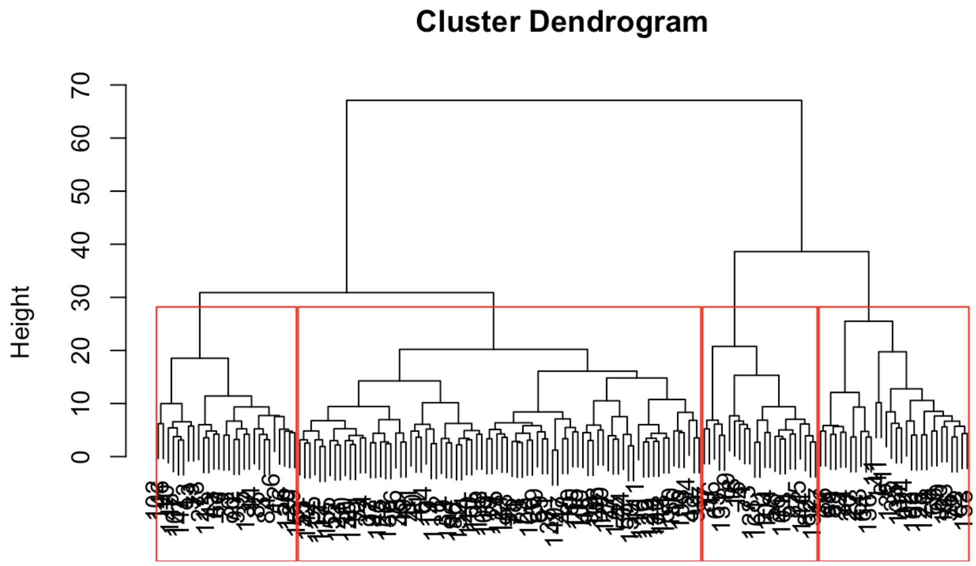


Table 5.3-1: distribution of the continuous variables across the 4 clusters. The results of the analysis of variance for continuous variables are also reported. In bold statistically significant comparisons.

Variable	**Cluster**	**Number**	**Mean**	**Std. Deviation**	p
Age	1	18	72.33	14.787	
	2	117	**78.74**	11.742	
	3	222	75.78	12.441	
	4	126	72.62	12.207	
	Total	483	75.55	12.391	**0.001**
Weight	1	18	78.3	11.3	
	2	117	**64.2**	12.1	
	3	222	72.7	11.9	
	4	126	76.8	10.1	
	Total	483	74.6	11.2	**0.001**
Height	1	18	1.69	.05	
	2	117	1.63	.07	
	3	222	1.66	.09	
	4	126	1.69	.07429	
	Total	483	1.71	0.06	**0.015**
BMI	1	18	**27.1**	3.9877	
	2	117	**20.3**	5.4260	
	3	222	25.6	3.8754	
	4	126	26.4	3.7531	
	Total	483	25.5	4.3157	**0.001**
NIHSS	1	18	6.33	6.532	
	2	117	7.85	6.094	
	3	222	6.68	6.231	
	4	126	6.79	6.958	
	Total	483	6.98	6.366	0.096
Barthel Index	1	18	**60.2**	39.2	
	2	117	**28.9**	27.5	
	3	222	40.2	29.1	
	4	126	43.4	6.7	
	Total	483	39.1	29.3	**0.020**
Hematocrit	1	18	36.9	5.3201	
	2	117	37.4	4.9022	
	3	222	38.7	4.1106	
	4	126	39.3	5.6868	
	Total	483	38.5	4.8168	**0.007**
Albumin	1	18	3.4	0.11	
	2	117	**2.9**	0.58	
	3	222	3.2	0.39	
	4	126	3.4	0.30	
	Total	483	3.2	0.44	**0.001**

Sodium	1	18	137.2	3.312	
	2	117	138.4	3.152	
	3	222	**139.4**	3.719	
	4	126	137.7	3.343	
	Total	483	138.7	3.529	**0.049**
Potassium	1	18	3.9833	.80104	
	2	117	4.1026	.68075	
	3	222	3.8797	.47686	
	4	126	3.9736	.61551	
	Total	483	3.9620	.58218	0.288
Glucose	1	18	109.7	21.584	
	2	117	**97.7**	24.645	
	3	222	102.5	33.813	
	4	126	**113.5**	32.192	
	Total	483	104.5	31.323	**0.001**
Total proteins	1	18	6.5	0.40	
	2	117	**6.1**	0.73	
	3	222	6.6	0.46	
	4	126	6.5	0.51	
	Total	483	6.5	0.57	**0.001**
Urea	1	18	38.00	11.027	
	2	117	48.64	29.064	
	3	222	43.42	18.594	
	4	126	43.52	16.848	
	Total	483	44.51	21.011	0.079
BUN	1	18	17.75	5.15	
	2	117	22.72	13.58	
	3	222	20.28	8.68	
	4	126	20.33	7.87	
	Total	483	20.79	9.81	0.090
Creatinine	1	18	.96	.29	
	2	117	1.03	.77	
	3	222	.94	.32	
	4	126	.98	.39	
	Total	483	.98	.48	0.456
BUN/Cr ratio	1	18	**18.7**	3.58	
	2	117	**24.6**	11.18	
	3	222	21.9	7.67	
	4	126	20.9	4.99	
	Total	483	22.2	8.10	**0.003**
Platelets	1	18	197.2	45.65	
	2	117	**283.1**	46.76	
	3	222	**166.5**	36.39	
	4	126	226.1	50.27	
	Total	483	211.4	63.92	**0.001**
Cholesterol total	1	18	199.7	27.55	
	2	117	**163.8**	34.58	
	3	222	170.4	32.81	
	4	126	**235.2**	37.43	
	Total	483	186.8	45.07	**0.001**
Cholesterol	1	18	179.8	59.627	

LDL	2	117	**93.9**	26.128	
	3	222	101.6	31.875	
	4	126	**154.1**	36.751	
	Total	483	116.4	42.801	**0.001**
Cholesterol HDL	1	18	**39.2**	5.456	
	2	117	51.59	16.139	
	3	222	50.41	14.374	
	4	126	49.45	19.661	
	Total	483	50.02	16.164	**0015**
Triglycerides	1	18	**356.2**	79.913	
	2	117	**89.5**	23.813	
	3	222	95.7	37.939	
	4	126	152.6	44.907	
	Total	483	118.8	66.145	**0.001**
Vitamin B12	1	18	**330.0**	81.162	
	2	117	**508.9**	386.929	
	3	222	394.4	181.488	
	4	126	357.6	140.228	
	Total	483	411.0	243.963	**0.041**
Folate	1		**10.2**	5.3500	
	2		9.9	8.4415	
	3		8.1	6.2687	
	4		**6.1**	2.4446	
	Total		8.0	6.2631	**0.041**
Homocysteine	1		**13.2**	3.7623	
	2		17.1	7.5416	
	3		**16.9**	8.2356	
	4		18.5	8.1900	
	Total		17.2	7.9486	**0.045**
Urine gravity	1		1.0162	.004717	
	2		1.0197	.009107	
	3		1.0191	.007798	
	4		1.0200	.006633	
	Total		1.0194	.007783	0.815
Length of enteral diet	1		0.67	1.53	
	2		3.00	6.26	
	3		2.34	5.15	
	4		3.00	5.80	
	Total		2.61	5.53	0.226

Table 5.3-2: distribution of the categorical variables across the 4 clusters. The results of the chi-square test is also reported. In bold statistically significant comparisons.

Variable	Cluster	Number			p
			Males	Females	
Gender	1	18	**12 (66.7%)**	6 (33.3%)	
	2	117	**21 (17.9%)**	**96 (82.1%)**	
	3	222	135 (60.1%)	87 (39.9%)	
	4	126	72 (57.1%)	54 (42.9%)	
	Total	483	240 (49.7%)	243 (50.3%)	**0.001**
			Yes	No	
Dysarthria	1	18	3 (16.7%)	15 (83.3%)	
	2	117	15 (12.8%)	102 (87.2%)	
	3	222	33 (14.9%)	189 (85.1%)	
	4	126	21 (16.7%)	105 (83.3%)	
	Total	483	72 (14.9%)	411 (85.1%)	0.969
			Yes	No	
Aphasia	1	18	3 (16.7%)	15 (83.3%)	
	2	117	39 (33.3%)	78 (66.7%)	
	3	222	48 (21.6%)	174 (78.4%)	
	4	126	18 (14.3%)	108 (85.7%)	
	Total	483	108 (22.4%)	375 (77.6%)	0.220
			Yes	No	
Diuretic drugs	1	18	9	9	
	2	117	51	66	
	3	222	54	168	
	4	126	36	90	
	Total	483	150	333	0.355
			Fois = 7	Fois < 7	
Oral intake	1	18	12	6	
	2	117	75	14	
	3	222	144	26	
	4	126	84	14	
	Total	483	105	56	0.864
			Yes	No	
Malnutrition	1	18	0 (0%)	18 (100%)	
	2	117	**42 (35.9%)**	75 (64.1%)	
	3	222	33 (14.9%)	189 (85.1%)	
	4	126	3 (2.4%)	123 (97.6%)	
	Total	483	78 (16.3%)	405 (51.7%)	**0.001**
			Yes	No	
Dehydration	1	18	6 (33.3)	12 (66.7%)	
	2	117	**63 (53.8%)**	54 (46.2%)	
	3	222	105 (47.3%)	117 (52.7%)	
	4	126	66 (52.4%)	60 (47.6%)	
	Total	483	240 (49.7%)	243 (50.3%)	0.307
			Yes	No	
Critical weight	1	18	0 (0%)	18 (100%)	

loss	2	117	**27 (23.1%)**	90 (76.9%)	
	3	222	9 (4.1%)	213 (95.9%)	
	4	126	0 (0%)	126 (100%)	
	Total	483	36 (7.5%)	447 (92.5%)	**0.001**
Dysphagia			Yes	No	
	1	18	6 (33.4%)	12 (66.6%)	
	2	117	30 (25.6%)	87 (74.4%)	
	3	222	57 (25.7%)	165 (74.3%)	
	4	126	24 (19%)	102 (81%)	
	Total	483	117 (24.2%)	366 (75.8%)	**0.004**